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ERYTHEMA INFECTIOSUM

REPORT OF AN EXTENSIVE EPIDEMIC

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Although there are numerous reports of erythema infectiosum in the literature, it appears to be a disease that is not well known. It is probably not rarely encountered in practice, but it is unrecognized as such and thus mislabeled. The occasion for discussing the subject again is the observation of a rather large epidemic of the disease in an orphanage in the city of New York, in which 80 children were affected, with a total of 170 attacks. Judging from the literature, there had been no previous epidemic of this condition in the city, although it has been observed elsewhere in the state (Hamburg and Elmsford).

Approximately fifty localized epidemics have been reported in the literature. However, there is no doubt that sporadic cases also occur.

HISTORICAL SURVEY

The disease was first described under the name "örtliche Rötheln" by Tschamer [1] in 1889, although he first observed the disease in 1886 and regarded it as a modified form of rubella. In the following few years several outbreaks were reported (Gumplowicz [2] and Tobeitz [3]), and in 1896 Escherich [4] expressed the opinion that it was a clinical entity. In 1899 Sticker [5] without knowledge of previous reports described the

1. Tschamer, A.: Ueber örtliche Rötheln, Jahrb. f. Kinderh. **29**:372, 1889.

2. Gumplowicz, L.: Casuistisches und historisches über Rötheln, Jahrb. f. Kinderh. **32**:266, 1891.

3. Tobeitz, A.: Zur Polymorphie und differential Diagnose der Rubeola, Arch. f. Kinderh. **25**:17, 1898.

4. Escherich, T.: Transactions of the Eleventh International Medical Congress, Moscow, 1896; cited by Shaw, H. L. K.: Am. J. M. Sc. **129**:16, 1905.

5. Sticker, G.: Die neue Kinderseuche in der Umgebung von Giessen (Erythema infectiosum), Ztschr. f. prakt. Aerzte **8**:353, 1899.

disease under the name of erythema infectiosum. Since then this name has been universally accepted, although in the interim descriptions of the disease have appeared under a variety of other names: *Ringelrötheln*, megalerythema epidemicum, fifth disease, *Grossflecken, exanthème variable,* erythema simplex marginatum, *epidemischen Kinder-Rotlauf,* erythema infantum febrile and erythema annulare in epidemic form.

The first epidemics were reported in Austria and Germany. Subsequently it appeared in France, Switzerland, the Netherlands, Norway, Italy, Rumania, Turkey, China and Uruguay. In the United States epidemics have occurred in the following cities: Hamburg and Elmsford, N. Y.; St. Louis,; Cleveland Heights, Ohio; Ogden, Utah; Branford, Conn. and San Francisco.

SYMPTOMS AND CLINICAL COURSE

Briefly, the sequence of events is as follows: Almost always the exanthem is the first symptom; rarely mild prodromal symptoms appear in the form of malaise, sore throat, coryza and fever.

Nearly always the rash first appears on one or both cheeks in the form of a bright red area; the appearance is as though the cheeks had been slapped. There is slight edema, and the cutaneous surface is smooth. The erythema stops abruptly at the nasolabial fold and the lower orbital border; occasionally it crosses the base of the nose, producing a butterfly configuration like that seen in lupus erythematosus. The cartilaginous portion of the nose and the circumoral area are always strikingly pale, the picture simulating in this respect that of scarlet fever. The posterior border of the erythema shades off gradually. In the mild attacks, the exanthem is superficial and fades rapidly; in the more severe, it acquires a deep cyanotic hue and regresses more slowly, feeling hot to the touch. The chin is seldom affected; the forehead, more often. The rash on the face usually lasts one to four days, although occasionally for several weeks. There is no enanthem, except sometimes mild redness of the throat and tongue or red macules on the hard or soft palate.

At times simultaneously, but usually within twenty-four to thirty-six hours after the onset on the face, an eruption appears on the extremities, especially the arms, but only in a portion of the cases. The extensor surfaces are commonly attacked. The palms and soles remain free. The gluteal region is frequently affected, while on the trunk, which often remains free, an erythema may appear resembling the rash of rubella. On the extremities, the eruption appears as discrete, minute, bright red macules, which gradually enlarge and may coalesce. Often the lesions become papular. Thus the rash may be morbilliform or scarlatiniform. As time progresses, the central portions of some lesions assume a violet color or fade completely; thus ringlike or garland-like

Classic appearance of erythema infectiosum on the third day, with intense erythema, crust formation and circumoral pallor.

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lesions are formed, as in erythema annulare or erythema gyratum. Occasionally by confluence of lesions a maplike appearance results. On the extremities the eruption usually remains from six to fourteen days, exceptionally up to twenty days; it may clear for hours or days only to reappear, either spontaneously or after slight local irritation. A peculiar cyanotic coloring, like cutis marmorata, may remain after the rash disappears. The rash may become arrested in any state of its progress.

Scaling, as a rule, is absent; however, a fine desquamation may occur on the face. Itching is absent. Slight adenopathy lasting for several days is sometimes present. The average temperature range is from 99.6 to 101 F., hardly ever higher. There are practically no general symptoms.

The blood picture is not characteristic. The leukocyte count is normal or decreased. Occasionally a lymphocytosis with a moderate increase in eosinophils may appear.

The prognosis is always good. No complications occur. Berberich [6] reported pains in the joints and Tripke [7] mild nephritis, but in their cases the diagnosis appears to have been incorrect.

Relapses occurring up to several months later have been reported as occurring frequently by Najzner,[8] Herrick [9] and others.

THE OUTBREAK AS OBSERVED IN THE INSTITUTION

At the time of the epidemic the institution housed a total of 137 children. There were 25 infants and children (boys and girls) 1 to 4 years of age occupying a separate floor, among whom not a single case occurred. None of these children was directly exposed to those affected, although the house help served the infected as well as the noninfected. Apparently the disease is not transmitted by carriers. The remaining 112 were divided into three groups, each group occupying a separate floor.

Group 1 consisted of 42 girls between the ages of 4 and 10 years. Of these 38 contracted the disease and 31 of the 38 had recurrences. The total of attacks for this group was 113. Four girls (9.5 per cent) remained well in spite of continuous exposure to the affected children.

6. Berberich, E.: Eine Epidemia von acutem Erythem bei Kindern in der Umgebung von Giessen (Erythema infectiosum acutum), Thesis, Giessen, von Münchow'sche Druckerei, 1899; cited by Shaw, H. L. K.: Am. J. M. Sc. **129**:16, 1905.

7. Tripke: Erythema infectiosum febrile oder epidemischer Kinderrothlauf, Kalender fur Frauen- und Kinderärzte, Kreuznach, 1901; cited by Shaw, H. L. K.: Am. J. M. Sc. **129**:16, 1905.

8. Najzner, cited by Tanon, L.; Cambessédès, M., and Lind, L.: La cinquième maladie ou mégalérythème épidémique, Paris méd. **87**:213, 1933.

9. Herrick, T. F.: Erythema Infectiosum: A Clinical Report of Seventy-Four Cases, Am. J. Dis. Child. **31**:486 (April) 1926.

Group 2 consisted of 40 boys between the ages of 6½ and 10 years. Of this group 30 contracted the disease. Including recurrences, the group had a total of 45 attacks. Ten boys (25 per cent) failed to contract the disease in spite of being continuously exposed.

Group 3 consisted of 30 boys between the ages of 4½ and 7 years. Of these 12 contracted the disease; none had a recurrence. Eighteen (60 per cent) were not affected.

The epidemic began on the afternoon of Nov. 4, 1941, following a stroll taken by a group of the children on the East River Drive. It was not an unusually cold, windy or wet day.

Group 1.—Soon after returning to the institution 4 of the girls in group 1 showed red cheeks and complained of some burning and pain. Subsequently, additional children showed symptoms as follows: 12 on November 6, 12 on November 7, 3 on November 8, 1 each on November 24 and December 9, 4 on December 19 and 1 on December 20.

The disease appeared without premonitory signs; the first symptom usually was a redness of one or both cheeks. The skin was uniformly rose red, as if it were wind burned or rouge had been applied. The area affected for the most part was the anterior half or third of each cheek. At this time there was definite sharp demarcation between the affected and the unaffected skin; this was especially true of the anterior border of the eruption. The areas were slightly elevated, and in the more severe attacks they were somewhat tender on pressure. On diascopic pressure the color disappeared, but it promptly returned on release of pressure. In the more severe attacks, on the day following the appearance of the eruption the center of the affected areas was rough to the touch, as if the surface had been scratched with a stiff brush, and the skin had assumed a cyanotic hue. Soon papules and vesicles appeared, which shortly thereafter became crusted; at this time the skin appeared eczematized. After this, the color faded; the crust persisted for a few days longer, eventually falling off, leaving a pinkish smooth surface. Marbling of the skin was occasionally seen. A few days elapsed before the skin was again normal. The entire cycle varied in duration from a day up to twelve days and averaged four days. When the disease was milder, the erythema varied in severity and color, usually showed no crusts and ran a shorter course, lasting only a day or two. Between these extremes, there were various gradations.

In 33 of the 38 affected children in group 1 the rash on the cheeks was symmetric. In 3 the eruption covered only part of one cheek. One girl had only a pea-sized papule in the center of each cheek; in still another eczematized areas occurred in these areas. In a number of cases the eruption faded, leaving an erythematous border. Seven-

teen of the patients had eruptions of the more severe type, as evidenced by the presence of small papules, vesicles and crusts within the flushed areas; these were either grouped or isolated, in some instances

TABLE 1.—*Primary Attacks and Relapses in Outbreak*

Group	No. of Children in Group	No. of Primary Attacks	Number of Relapses per Patient							Total of Relapses
			0	1	2	3	4	5	6	
1. Girls 4 to 10 yr. of age	42	38	7	5	13	10	2	0	1	
Actual number of relapses			0	5	26	30	8	0	6	75
2. Boys 7 to 10 yr. of age	40	30	16	13	1	..	..	..	..	
Actual number of relapses			0	13	2	..	..	..	..	15
3. Boys 4½ to 7 yr. of age	30	12	12	..	..	..	..	..	..	
Actual number of relapses			0	..	..	..	..	..	..	0
4. Infants and children 1 to 4 yr. of age	25	0	..	..	..	..	..	..	..	
Total	137	80	35	18	14	10	2	0	1	90
Total number of primary attacks and relapses										170

TABLE 2.—*Dates of Onset and Number of Attacks*

Primary Attacks		Relapses	
Date	Number	Date	Number
Nov. 4, 1941	4	Nov. 23, 1941	3
6	12	24	17
7	12	24	3
8	3	27	1
9	5	Dec. 6	5
10	15	7	1
11	4	8	1
12	4	9	12
16	11	12	1
24	1	14	14
Dec. 9	1	16	2
14	2	17	2
19	4	18	3
20	1	19	2
Jan. 22, 1942	1	Jan. 5, 1942	3
		6	3
		7	2
		8	10
		24	4
		Feb. 1	1
		Mar. 22	1
Total	80	Total	90

resembling scratch marks. These changes usually appeared on the second day or later and lasted several days. Most of the children showed roughness of the affected skin and subsequently slight desquamation. In 2 the chin was likewise affected. In 2 others the eruption extended across the bridge of the nose. In only 6 of this group were lesions present elsewhere than on the face. One had many discrete, skin-colored papules on the arms, chest, abdomen and back; these lasted but a single day. One patient exhibited a quarter-sized macule,

of port wine color, on each leg and scattered erythematous macules on both forearms (these appeared on the third day and lasted one day); an unusual feature of this girl's eruption was that eventually the affected area on the left leg showed some desquamation. One patient showed a faint flush on the chest, which was, however, patchy on the abdomen and lasted two days. The fourth had a mild scarlatiniform rash on the chest and upper part of the abdomen lasting two days, and later one red papule appeared on the abdomen. The fifth presented a hemorrhagic lesion resembling those of erythema multiforme, 1 by ⅔ inch (2.5 by 1.7 cm.) in size, on the extensor surface of the left leg; this appeared on the third day and lasted several days. The sixth had no flush on the face but a morbilliform eruption on the forearm, less evident on the thighs. It is of interest to relate that this patient in a subsequent relapse showed the typical facial eruption.

It is noteworthy that there were almost no constitutional symptoms except for a slight elevation in temperature up to 100.4 F. (which was not necessarily associated with the most severe eruption), mild congestion of the throat, in some cases slight enlargement of the papillae of the tongue and slight enlargement of the cervical glands. These symptoms lasted from one to several days.

No medication was found necessary for children in this group or any of the others.

Relapses in group 1: Of the 38 patients, 31 had relapses. Five of the 31 patients had 1 relapse, 13 had 2 relapses, 10 had 3 relapses, 2 had 4 relapses and 1 had 6 relapses. The total number of relapses was 75.

The interval between relapses varied from two to forty days. The duration of the attacks varied from one to twenty-five days and averaged nine days.

In 72 of the 75 relapses both cheeks were affected at the outset, and in 35 of these the eruption was severe. Of the remaining 3 relapses, in 1 the eruption first appeared on the body and involvement of the cheek followed; in 2 the eruption appeared only on the extremities. In 5 attacks the lower part of the chin was affected. In 1 the eruption was herpes-zoster-like in distribution and was located on the upper part of the right thigh, the face remaining unaffected. In 38 of the 72 instances of eruption on the cheeks, no lesion on the body was observed. In the remaining 34 the following regions either alone or in several areas were involved: 6, the chest; 15, the abdomen; 14, both forearms; 1, the left forearm; 2, the elbow; 7, the back of one or both hands; 1, the wrist; 2, both cubital spaces; 3, the left cubital area only; 1, the right arm; 2, both axillas; 1, a shoulder; 4, both thighs, and 2, the neck in a necklace-like arrangement.

Concerning the eruptions, it may be stated that for the most part they were a counterpart of what has been described in typical cases, consisting of: erythema of varying intensity (diffuse and sometimes punctate), macules, papules (discrete as a rule), vesicles and crusted lesions, at times linear (Köbner phenomenon?), also morbilliform, annular (erythema-multiforme-like) and purpuric lesions. There were occasional marbling and cyanosis, which at times persisted for days or weeks.

The affected areas were either sparsely or extensively involved. Although the eruption was short lived (lasting one or two days), there was a tendency in some instances for recurrence of the same type and pattern of eruption or of a different one.

As noted, scarlatiniform eruptions were observed. In 3 of these, the Schultz-Charlton reaction test proved negative.

The concomitant symptoms paralleled those already mentioned, except that in a few of the relapses the temperature mounted to as high as 101.2 F. Patients with such a temperature were kept in bed for twenty-four hours, as a precautionary measure.

Group 2.—In the group of 40 boys between the ages of 6½ and 10 years, 30 had the disease. In 4 the symptoms appeared on November 9, in 16 on November 10, in 4 on November 11, in 4 on November 12 and in 2 on December 14. The duration varied from one to ten days; the average was five days.

In 25 patients both cheeks were affected; in 4, the left cheek alone and in 1, only the right cheek. In 14 of these 25 the eruption was limited to the face; hence 11 had in addition the eruption on the body observed in some of the patients in group 1.

Relapses in group 2: Of the 30 boys, 14 had relapses. Thirteen had 1 relapse and 1 had 2 relapses.

The average intervals between attacks varied from twenty-five to thirty-three days. The average duration of the relapses was three days.

In 9 patients both cheeks were affected; in 4, the left only, and in 2, only the right. Four boys had some vesiculation and crusting. In 2 patients both forearms, and in 2 only the left forearm, showed a diffuse punctate erythematous rash. In 1 there was a punctate rash on the buttock.

Group 3.—In this group of 30 boys, between the ages of 4½ and 7 years, 12 had the disease. In 11 the eruption appeared on November 16 and in 1 more than two months later, on Jan. 22, 1942.

In 1 boy only the left cheek was affected; in all the others, both cheeks. In another patient the helix of each ear and the chin showed a morbilliform rash. Six patients had vesicles and crusts in the affected area. One had a slight punctate rash on the chest. The rash lasted from one to three days, and there was not a single relapse.

LABORATORY DATA

Specimens of urine were repeatedly examined during the period of the outbreak and were found normal.

Blood counts showed a slight leukocytosis. In a few cases there was a slight increase in the polymorphonuclear leukocytes and eosinophils.

A section of the skin studied at the Rockefeller Research Laboratory by Dr. Joseph E. Smadel was reported on as follows:

> Patchy exudate is present on the surface. Proliferation of epithelial cells is evident from the thickening of the derma and from the increased number of the mitotic figures. Here and there epithelial cells are swollen and have large clear nuclei with several prominent nucleoli. Several small vessels in the deeper layers of the skin are surrounded by various cuffs of mononuclear cells. Inclusion bodies are not seen.

Cultures of scrapings from lesions in 8 cases showed a fungus resembling a trichophyton in 1 case only. In all the 8 cases one or more of the following organisms were found on Loeffler's culture medium: Staphylococcus albus, Staphylococcus aureus, a gram-negative diplococcus and a gram-positive bacillus (Dr. John T. Meyers).

The heterophile antibody test for infectious mononucleosis (Dr. Annis E. Thompson) was performed in 5 cases. In 4 the reaction proved negative, and in 1 the test showed 1 : 14, 1 : 0 and 1 : 14 agglutination (Forssman antibody, not that of infectious mononucleosis). Agglutination tests for typhoid, paratyphoid A and B, brucellosis and typhus (Bacillus proteus X 19) were made in 5 cases (Board of Health Laboratory), with negative results.

On Feb. 10, 1942 Dr. Joseph E. Smadel, of the Hospital of the Rockefeller Institute for Medical Research, made the following report:

> The results of our studies on the children with erythema infectiosum may be summarized as follows:
>
> *Part 1. Animal Inoculations.*—Throat washings obtained from 2 girls on Dec. 12, 1941 were pooled. The fluid contained many bacteria, which consisted for the most part of organisms which apparently belonged to the group of alpha hemolytic streptococci, with a few gram-negative cocci. A portion of the fluid was shaken with a small amount of ethyl oxide (ethyl ether) and stored for one hour at ice box temperature, after which the ether was removed. The culture on the ethyl oxide–treated throat washings showed no growth.
>
> Two rabbits were inoculated with untreated washings on the scarified cornea and were given 1 cc. of the same material intranasally. They were also inoculated intraperitoneally with 2 cc. of the ethyl oxide–treated throat washings. Six mice, 2 Syrian hamsters and 2 guinea pigs were inoculated intraperitoneally with ethyl oxide–treated washings, and untreated washings were instilled into their noses. None of these animals showed obvious disease during the subsequent month of observation.

Specimens of heparinized whole blood were each inoculated intraperitoneally into 2 guinea pigs. Cultures of the blood failed to show bacterial growth. The guinea pigs remained well.

Summary: Throat washings and whole blood taken from 2 patients during the early part of a recurrent attack of erythema infectiosum failed to produce the disease when inoculated into rabbits, guinea pigs, hamsters and mice.

Part 2. Cultures of Material from Throats of Children at the Orphanage.—On Dec. 20, 1941, throat cultures were made of material from the throats of 21 children in the home. The children were grouped as follows: 7 girls with a third attack; 4 boys with a second attack; 4 boys without evidence of disease who had had erythema infectiosum in November, and 6 boys who had never had the disease. Swabs were streaked immediately on human blood-agar plates. No significant difference was noted in the cultures for the four groups of children. A mixed flora was found in each culture. The predominant organism in practically all the cultures was a gram-positive coccus which apparently belonged to the group of alpha hemolytic streptococci. The significance of these observations is not apparent. Two boys, both convalescent, were found to have beta hemolytic streptococci.

DIFFERENTIAL DIAGNOSIS

The diagnosis of erythema infectiosum is not difficult. It is apparently often missed because the disease is not sufficiently well known. Once seen, it is never forgotten; the facial eruption is so strikingly characteristic, showing the symmetric erythema which resembles slapped cheeks. Further distinguishing features are: its occurrence in epidemics; the mild general symptoms; its almost constant appearance first on the cheeks and often only there; the distribution; the distinct progression and evanescence of the rash; the lack of complications, and the frequent relapses, resulting in a long course. If one bears these features in mind, all the exanthems and also multiform erythema (toxicoderma due to drugs, foods, bacteria or other allergens) and dermatitis due to external agents can easily be excluded.

Not even erythema multiforme of Hebra, so frequently stressed in the earlier literature, need cause confusion. In our cases there was little resemblance. Erythema multiforme of Hebra rarely appears in epidemics; it is frequently accompanied by general symptoms, at times severe; the eruption first appears and is most characteristic on the backs of the hands and feet, and the lips and buccal mucosa are not infrequently affected.

EPIDEMIOLOGY

The disease is undoubtedly infectious, most often appearing as group or family infections during epidemics. Hilmi [10] reported an outbreak in Constantinople (1930) during which many afflicted persons were seen on the streets and in the schools. Sporadic cases do occur. Chil-

10. Hilmi, I.: Megalerytheme (sog. 5 Krankheit), Monatschr. f. Kinderh. **50**:340, 1931.

dren in the school years are especially predisposed. Adults and children of preschool age are infrequently attacked. The disease is observed in both sexes, but predominantly in females.

The small number of cases, short duration of individual attacks and infrequency of outbreaks point to a lack of susceptibility. Usually not all the children of a family become infected. However, contrary to the consensus, Herrick [9] stated that the contagiousness is rather high. The total duration of most epidemics has been no longer than several months, and the peak is reached in a few weeks. There is no definite season; it is most frequently observed in the following order: spring, summer and winter.

The mode of transmission is unknown. Most observers favor droplet infection. However, investigations utilizing cultures and inoculations of animals with secretions from the nose and throat (Herrick,[9] Lawton and Smith [11] and Rector [12]) were unsuccessful in detecting the causative agent; nor has the disease been reproduced. Herrick [9] and Taccone [13] stated the belief that recovery from an attack (including relapses) confers immunity. The duration of infectivity is not known. The disease runs such a mild course that patients need not be isolated, except perhaps in institutional outbreaks. Thus far, the disease is not one that is reportable. However, it should be so made in order that a better opportunity may be afforded to study it.

The incubation period is stated as two to twenty-one days, usually from nine to fourteen days (Zuckerman [14]).

SUMMARY AND CONCLUSIONS

An outbreak of erythema infectiosum, lasting from Nov. 4, 1941 to April 11, 1942, in an orphanage in New York city is reported. The institution housed 137 children; of these 80 were attacked.

Eighty primary attacks and 90 relapses were observed, making a total of 170 attacks.

In individual cases the relapses numbered from 1 to 6. Eighteen patients (22.5 per cent) had 1 relapse; 14 (17.5 per cent) had 2; 10 (12.5 per cent) had 3; 2 (2.5 per cent) had 4; 1 (1.2 per cent) had 6, and 35 (43.8 per cent) had none.

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11. Lawton, A. L., and Smith, R. E.: Erythema Infectiosum: A Clinical Study of an Epidemic in Branford, Conn., Arch. Int. Med. **47**:28 (Jan.) 1931.

12. Rector, J. M.: Erythema Infectiosum: Clinical Observations During an Epidemic, J. Pediat. **15**:541 (Oct.) 1939.

13. Taccone, G.: Un epidemia di "quinta mallattia" (eritimo infettivo), Riv. di clin. pediat. **25**:145, 1927; abstracted, J. A. M. A. **88**:2005 (June 18) 1927.

14. Zuckerman, S. N.: Erythema Infectiosum with Report of an Epidemic in San Francisco, Arch. Pediat. **57**:168 (March) 1940.

The largest number of children with the disease, the most severe attacks and the greatest number of relapses were among the girls. Next in order of frequency and severity of attacks were the group of older boys. The mildest attacks occurred among the younger boys; moreover, no relapses were observed in this group.

In 64.7 per cent of the children attacked the eruption was limited to the face; in 2.3 per cent it was limited to the body, and in 33 per cent the face and the body were affected.

Infants and children between the ages of 1 and 4 years appeared to be relatively immune.

Seventy of the 80 primary attacks occurred within the first thirteen days following the outbreak. The relapses appeared in cycles.

Extensive laboratory and epidemiologic studies failed to throw any light on the causation.

In the public school attended by the affected children not a single case of the disease occurred.

The disease is apparently not transmitted by carriers.

The disease is not reportable, but it should be so made to make possible etiologic and epidemiologic studies.

The incubation period in this epidemic appears to have been from one to twelve days.

The disease offers no diagnostic difficulties, since the facial eruption is characteristic.

When there is no facial eruption the disease cannot be clinically diagnosed when it occurs sporadically. However, during epidemics even this form can be readily diagnosed.

1 West Eighty-Fifth Street.

124 East Fortieth Street.

317 East Seventeenth Street.

INJECTIONS OF GOLD SODIUM THIOSULFATE PLUS ULTRAVIOLET IRRADIATION

EFFECTS OF CONCURRENT INTRADERMAL OR INTRAMUSCULAR INJECTIONS OF GOLD SODIUM THIOSULFATE AND ULTRAVIOLET IRRADIATION ON EXPERIMENTAL ANIMALS

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The subject of chrysiasis, or gold pigmentation of the skin, following exposure to ultraviolet radiation has recently been reviewed.[1] In all cases reported the condition followed intravenous injections of gold salts, principally sanocrysin (gold sodium thiosulfate), in large doses, totaling 150 mg. of gold sodium thiosulfate per kilogram of body weight or more. Whether this pigmentation might result from the intradermal or intramuscular administration of gold sodium thiosulfate has never been observed or experimentally tested. Schamberg,[2] however, described pale blue staining of the skin of 1 patient and 1 rabbit following the subcutaneous infiltration of a colloidal gold solution.

Chrysiasis has not been produced in experimental animals, although intradermal and subcutaneous deposition of gold granules following the intravenous injection of massive doses of gold salts into mice, guinea pigs, rabbits and dogs [3] has been shown histologically and chemically.

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From the Department of Dermatology and Syphilology and the Institute of Pathology of Western Reserve School of Medicine and of the University Hospitals of Cleveland.

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2. Schamberg, J. F.: Chrysoderma: A Permanent Gold Staining of the Skin, Arch. Dermat. & Syph. **18**:862 (Dec.) 1928.

3. (*a*) Kurosu, S.: Ein histochemischer Goldnachweis, zugleich ein Beitrag zur Frage der Verteilung und Ausscheidung des Sanocrysins im gesunden und tuberkulösen Körper, Ztschr. f. d. ges. exper. Med. **57**:77, 1927. (*b*) Brahn, B., and Weiler, G.: Die quantitative Verteilung des Goldes in den Organen gesunder und tuberkulöser Kaninchen nach Behandlung mit Goldpräparaten; versuche an nicht tuberkulösen Kaninchen, Biochem. Ztschr. **197**:343, 1928. (*c*) Henius, K.,

(Footnote continued on next page)

Kochs [4] experimentally produced local chrysiasis by the ultraviolet irradiation of nonpigmented skin on the trunk of a patient suffering from chrysiasis of the exposed parts.

Intradermal injection of gold sodium thiosulfate in the therapy of lupus erythematosus was introduced by Monash and Traub [5] in 1931. A 1 per cent aqueous solution was employed, using doses of 10 to 25 mg. weekly. Any swelling that took place was controlled by ice packs. Recently one of these authors [6] reported having given between five hundred and one thousand intradermal injections of the 1 per cent aqueous solution of gold sodium thiosulfate, introducing only a few minims into each of several areas at two to three week intervals; the clinical results have been "fairly satisfactory," and no sloughing or scarring was observed.

Intramuscular injection of gold salts was tried experimentally on guinea pigs by De Witt, Cadwell and Leavell [7] in 1918, using aurous cyanide (Au CN), auric cyanide ($Au(CN)_3$), gold potassium cyanide ($Au\ K(CN)_2$) and "aurocantan (cantharidyl ethylenediamine aurous cyanide)." These salts were readily absorbed, no more remaining in the injected tissues than in other parts of the body. No untoward reactions to the injections were described. Forestier [8] in 1929 popularized the intramuscular method of administration of gold salts clinically by using myochrysine (sodium aurothiomalate) in the treatment of rheumatoid arthritis. Other authors [9] using this drug reported many cases of local reactions (e. g. pain and local induration) and various cutaneous eruptions; no case of chrysiasis was observed.

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5. Monash, S., and Traub, E. F.: Modification of Therapy with Gold Compounds in Lupus Erythematosus: Preliminary Communication, Arch. Dermat. & Syph. **24**:110 (July) 1931.

6. Traub, E. F.: Personal communication to H. N. Cole.

7. De Witt, L. M.; Cadwell, S. M., and Leavell, G.: Distribution of Gold in Animal Tissues: Studies on the Biochemistry and Chemotherapy of Tuberculosis, XVII, J. Pharmacol. & Exper. Therap. **11**:357, 1918.

8. Forestier, J.: L'aurothérapie dans les rheumatismes chroniques, Bull. et mém. Soc. méd. d. hôp. de Paris **53**:323, 1929; Rheumatoid Arthritis and Its Treatment by Gold Salts: Results of Six Years' Experience, J. Lab. & Clin. Med. **20**:827, 1935.

9. (*a*) Key, J. A.; Rosenfeld, H., and Tjoflat, O. E.: Gold Therapy in Proliferative (Especially Atrophic) Arthritis, J. Bone & Joint Surg. **21**:339, 1939. (*b*) Phillips, R. T.: The Treatment of Arthritis with Gold Salts, New England J. Med. **214**:114, 1936. (*c*) Lintz, R. M.: Toxic Reactions with Gold Salts in the Treatment of Rheumatoid Arthritis, J. Lab. & Clin. Med. **26**:1629, 1941.

Experimentally, Koppenhöfer,[10] Fleischmann[11] and Block, Buchanan and Freyberg[12] injected various gold preparations intramuscularly into white rats and guinea pigs. They consistently found that the absorption of gold compounds after intramuscular administration was directly related to the solubility of the compounds. Employing chemical analytic methods they found that only 1.4 to 7.6 per cent of water-soluble gold compounds remained at the injection site twenty-four hours after daily injections for two weeks while 21 to 83 per cent of colloidal gold preparations was retained at the site of injection. When oil suspensions of gold compounds were used, histiocytes were found to take up the metallic salt.

Steinbrocker[13] listed gold sodium thiosulfate, myochrysine, solganol B oleosum (aurothiodextrose) and myoral (calcium aurothioglycolate) as drugs which clinically may be employed either subcutaneously or intramuscularly.

PURPOSE OF STUDY

Using moderate doses of gold sodium thiosulfate (1 mg. per kilogram of body weight), comparable to those used in human therapy, we pursued this experimental study to determine:

(1) If chrysiasis would result following intradermal or intramuscular injections and concomitant ultraviolet irradiation of the injected area; (2) if the gold would be microscopically demonstrable at the injection site, and (3) what gross and microscopic pathologic changes would result in the skin following such treatment.

METHOD OF STUDY

Healthy young albino rabbits and white-bodied guinea pigs of both sexes were employed.

Experiment 1.—In this preliminary experiment the erythema time of ultraviolet irradiation for the closely clipped (using medium tooth, electrically driven

10. Koppenhöfer, G. F.: Ablagerung und Verteilung von Gold nach Zufuhr anorganischer und organischer Goldpräparate, Deutsche med. Wchnschr. **62**:1011, 1936.

11. Fleischmann, R.: Ueber die Grundlagen der modernen Goldtherapie, Ergebn. d. Hyg., Bakt., Immunitätsforsch. u. exper. Therap. **23**:125, 1940.

12. Block, W. D.; Buchanan, O. H., and Freyberg, R. H.: Metabolism, Toxicity and Manner of Action of Gold Compounds in the Treatment of Arthritis: II. A Comparative Study of the Distribution and Excretion of Gold Following the Intramuscular Injection of Five Different Gold Compounds, J. Pharmacol. & Exper. Therap. **73**:200, 1941.

13. Steinbrocker, O.: Arthritis in Modern Practice: The Diagnosis and Management of Rheumatic and Allied Conditions: With Chapters on Painful Feet, Posture and Exercises, Splints and Supports, Manipulative Treatment and Operations and Surgical Procedures, by John G. Kuhns, Philadelphia, W. B. Saunders Company, 1941.

animal clippers) backs of guinea pigs and rabbits were determined. The source of ultraviolet radiation was a quartz mercury vapor lamp (Hanovia brand, Luxor model) set at 30 inches (76 cm.) above the surface of the skin.

Successive thirds of the clipped area on the back of each of 2 guinea pigs and 2 rabbits were exposed for two, four and six minutes. Only the six minute areas on all the animals showed a barely perceptible erythema after twelve hours. Therefore it was decided to employ five minute (suberythema) exposures in the main experiment.

Experiment 2.—Fifty-two animals were used, 26 of each species. Two large groups received 1 mg. per kilogram doses of gold sodium thiosulfate by the intradermal or intramuscular route at weekly intervals for ten weeks. Concurrent daily suberythema doses of ultraviolet radiation (as determined in experiment 1) were administered to each animal, and the skin of the back was kept bare by weekly or thrice weekly close clipping. At no time was the hair on the back longer than 1.0 to 1.5 mm., and the pink skin was always clearly visible. The daily irradiation was continued for one week after the last (tenth) injection.

After ten weeks of treatment the animals were observed for an additional month and then killed; autopsy and histologic examination of the treated areas were performed. The injection sites of those animals succumbing during the experimental period were preserved in solution of formaldehyde; a few of these animals were not usable, having been partially eaten by cage mates or having undergone varying degrees of autolysis when dying during a week end.

The animals were weighed weekly throughout the course of the experiment to determine accurate dosage of the gold sodium thiosulfate for each injection.

Suitable controls were employed, with omission of either the ultraviolet exposures or the injections of gold sodium thiosulfate or with substitution of injections of distilled water in volumes equal to those of the gold solution used in the main body of the experiment.

The animals were disposed into the following groups:

	Guinea Pigs	Rabbits
a. Gold compound (intramusc.) + ultraviolet rays.....	10	9
b. Gold compound (intraderm.) + ultraviolet rays.....	10	9
c. Gold compound (intramusc.) alone.....	2	2
d. Gold compound (intraderm.) alone.....	2	2
e. Water (intraderm.) + ultraviolet rays.....	2	2
f. Ultraviolet rays alone	..	2
Totals	26	26

Technic of Injections.—A 0.2 per cent solution of gold sodium thiosulfate was used. It was freshly prepared just before each series of injections with sterile distilled water. This dose (1 cc. contains 2 mg. of the gold salt) was selected because it was easily and accurately measurable yet did not raise too large a wheal or bleb on being injected. The site of injection in each case was paravertebral in the lower right lumbar region, since this area was easy to irradiate, the vertebrae were constant landmarks to insure repeated injections into the same site and it was difficult for the animal to bite or scratch the area.

The injections (0.13 to 0.43 cc. in the guinea pigs and 0.78 to 1.53 cc. in the rabbits, depending on the body weight) were presumably painful to some degree; the intracutaneous injections of the gold salt caused the guinea pigs to squeal

and the rabbits to writhe vigorously during the administration. The injections of water caused far less discomfort. Intramuscular injections of the solution of gold sodium thiosulfate caused extension of the ipsilateral thigh and tonic rigidity of the limb for a few seconds to two minutes in most of the guinea pigs and tonic rigidity of the injected lumbar muscles for a few seconds in most of the rabbits.

GROSS CHANGES

There was no visible local or diffuse change in the skin at any time during the course of intramuscular injections in either the guinea pigs or the rabbits.

Immediately following the intradermal injections of the solution of gold sodium thiosulfate a pinkish wheal or bulla was observed. This resolved into an area of erythema two or four hours later. In twenty-four hours this became a slightly smaller zone of blotchy ecchymosis, and in four or five days the area was covered by a dark brown to black dry crust in all of the animals. One week after the injection this crust had dropped off in the majority of cases, revealing a 0.5 to 5 mm. pink, slightly depressed scar. With the larger animals this crust remained ten to twenty days before separating; in only 1 guinea pig was there pus formation beneath one of the crusts.

Since each succeeding injection was placed as closely as possible to the one preceding, each animal surviving the series of injections displayed a rosette of white to pink cicatrices over his right lumbar region. On 1 guinea pig there remained a 22 by 13 mm. dry black crust in the injection area at the end of the observation period.

In the cases of the intradermal injections of distilled water (0.5 cc. of water per kilogram of body weight) the wheals were more transitory, lasting one-half to two hours; the erythema and ecchymosis were fleeting (one to two days), and in only the 2 guinea pigs did some small (0.5 to 1.5 mm.) white scars remain. The two rabbits similarly inoculated showed no gross evidence of cutaneous damage at the end of the observation period.

In none of the animals exposed to ultraviolet radiation or kept as controls in a darkened stock room was any abnormal pigmentation observed during the course of the experiment.

Each animal found dead or killed (by a blow on the head at the conclusion of the experiment) was immediately subjected to autopsy, but gross examination failed to reveal any characteristic visceral changes.

Twenty-eight animals, 14 of each species, survived the entire experiment and were then killed. However, pathologic material from a total of 44 of the 52 animals was available and studied microscopically.

HISTOLOGIC STUDY

Gold granules in the skin taken from cases of chrysiasis have been readily demonstrated [14] by ordinary fixation in solution of formaldehyde and routine staining methods to be deposited as irregularly sized black granules in free and fixed macrophages, blood and lymph vessel wall cells and occasionally free in the corium. Dark field illumination [15] showed these deposits as brilliant flecks of light. Kurosu [3a] and others have described other fixation and staining methods.

From each animal of this experimental series suitable for study (i. e., not eaten by cage mate or decomposed) the entire treated area was removed, including skin, fascia and muscle down to the underlying bone. This tissue was immediately placed in solution of formaldehyde U.S.P. diluted 1:10 and hardened for one or more weeks. Sections passing directly through the involved area were then cut on the microtome and mounted unstained and also stained by the routine hematoxylin-eosin method.

Each series of sections was examined by means of the "high dry (450 ×)" oil immersion lens (1,000 and 1,600 ×) and by the oil immersion lens and dark field condenser system.

Stained sections from the control (no injections and injections of water) animals showed normal guinea pig and rabbit skin, hair, cutaneous appendages, connective tissue and striped and smooth muscle tissue. The stained section from the skin of a guinea pig inoculated intradermally with water passed directly through two areas of subepidermal fibrosis which were relatively avascular (scar tissue). There was no inflammatory reaction.

In the cases of 5 animals (2 guinea pigs and 2 rabbits which were irradiated and 1 rabbit which was not irradiated) inoculated intradermally with gold sodium thiosulfate the sections passed through areas of subepidermal fibrosis which showed no perivascular or interstitial cellular infiltration. In only 2 rabbits (1 dying after the second intramuscular injection of the gold compound, the other completing the series of intracutaneous injections) was a sparse infiltration of round cells found in the subepidermal layer.

Sections of the skin and subcutaneous tissues from 4 rabbits which became ill and died after four to ten intracutaneous injections of gold sodium thiosulfate (irradiated series) showed green to black clumps

14. (*a*) Zimmerli, E., and Lutz, W.: Eine eigenartige Form von Pigmentierung nach Goldbehandlung, Arch. f. Dermat. u. Syph. **157**:523, 1929. (*b*) Borchardt.[3d] (*c*) Wigley, J. E. M.: Some Observations on the Deposition of Gold in the Skin, Brit. J. Dermat. **44**:69, 1932.

15. Cascos, A.: Étude comparative des pigmentations métalliques: Argyrose et chrysose, Ann. de dermat. et syph. **7**:751, 1936.

and groups of coccic forms and some "cigar packet" clusters of short bacillus forms. These bacteria were present in phagocytic cells near small blood vessels, within blood vessels, free in a thrombus and subjacent to an infected scar. No granules described in the literature as characteristic of gold deposition were found in any of the sections.

By dark field technic unstained sections of skin and subjacent tissues from all the available animals were examined. In addition, the preceding hematoxylin-eosin sections were also examined by this method. The control sections showed the stratum corneum as a rather bright line above a dully glowing stratum mucosum. The hair shafts and stripped-off corneal layers occasionally contained some bright streaks, and oil droplets were distinguished in the sebaceous glands.

The corium and subcutaneous connective tissue were made up of wavy scintillating white fibers, while small vessels were dark and were made out with difficulty. The bundles of striated muscles were rather dull, although the sheath nuclei could be seen. There were occasional large round bright masses seen throughout the corium, and some were not in the same plane as the section; these were interpreted as entrapped small air bubbles. In other sections tan-colored granules were scattered throughout and also away from the tissue; these apparently were dust or particles of nonaurous precipitate.

In sections from the animals intradermally and intracutaneously inoculated with solution of gold sodium thiosulfate the structures all appeared as described. The areas of fibrosis were less luminous than the unaffected corium. Bacterial masses appeared light tan in color. No interstitial or perivascular brilliant granules, described as characteristic of gold deposition, were found in any of the sections.

CONCLUSIONS

1. Under the conditions of the experiment (i. e., doses comparable to those used in human beings, given weekly for ten weeks) neither intradermal nor intramuscular injections of gold sodium thiosulfate solution produced chrysiasis in guinea pigs or rabbits when concurrent ultraviolet radiation was administered.

2. Intradermal injections of a 0.2 per cent aqueous solution of gold sodium thiosulfate invariably resulted in permanent scar formation in guinea pigs and rabbits, without relation to exposure to ultraviolet radiation, when given in doses of 1 mg. of gold sodium thiosulfate per kilogram of body weight.

3. Intramuscular injections of a 0.2 per cent aqueous solution of gold sodium thiosulfate produced no gross or microscopic changes in the animals studied.

4. No deposition of gold in the skin or subcutaneous tissues of the guinea pigs or rabbits was detectable either in routinely stained sections or in unstained sections examined by the dark field technic.

5. This study offers additional evidence that the clinical administration of gold sodium thiosulfate might safely be tried by the intramuscular route. However, the intradermal injection of this salt into man, if attempted, should be in but small amounts and with great circumspection.

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HEREDITARY DYSTROPHY OF THE HAIR AND NAILS

REPORT OF A CASE

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In the past twelve months the opportunity to see all the cutaneous diseases referred to a station hospital from two Army divisions in training at one military reservation, the troops from a reception center and troops stopping in transit has enabled one of us (C. S. L.) to observe a number of comparatively rare dermatoses in soldiers. These have included: (1) tuberculoid leprosy, (2) xanthoma diabeticorum, (3) acquired ichthyosis, (4) erythroplasia of Queyrat, (5) glossitis rhombica mediana (2 cases), (6) symmetric erythema of the soles, first described by Pernet (12 cases) and (7) hereditary dystrophy of the hair and nails.

Because of certain interesting features, the last-mentioned disease is the subject of this discourse.

REPORT OF CASE

The patient was a 21 year old white soldier of Slavic ancestry who was referred to this hospital from the medical dispensary of his infantry organization with a tentative diagnosis of "fungous infection of the nails." That this should have been his first outpatient visit in his thirteen months of army service might seem unusual except that prior to his admission to the hospital he had been transferred from a warm to a comparatively cold climate, and his hands, previously in fair condition, were aggravated by exposure to cold weather incidental to a vigorous outdoor training program. The soldier stated that in addition to the changes in his nails he had always noted a sparseness of hair growth, particularly from the onset of puberty. He did not consider his difficulty unusual, inasmuch as it had been present in other generations of his family. For a number of years he had worked in civilian life as a construction laborer and apparently was able to preserve a satisfactory degree of comfort and integrity of his finger tips by exercising care in his work. Several times, however, there had been episodes of subungual infection with purulent discharge, yet none had occurred during his army service prior to his admission to this hospital.

The patient was well developed, muscular and vigorous, the results of his physical examination being essentially normal with the following exceptions:

1. Nails: The nails of the fingers were partly separated and raised from the nail beds; they were brittle, atrophic, longitudinally striated and curved

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transversely. They were stunted and perhaps half their expected length. At the time of the patient's admission to the hospital the tips of the fingers were exquisitely tender and from beneath the nails a yellow seropurulent material could be expressed on slight pressure. There was evidence of hyperkeratosis of the nail beds. The finger tips, though thickened and hyperkeratotic, were painful by reason of deep, raw, stellate fissures. In addition, the toe nails were stunted and thickened but showed no evidence of secondary infection, nor had the tips of the toes undergone the same atrophic changes as had the finger tips.

2. Hair: There was a decided paucity of hair of the head, chest, axillas and groins. Such hair as was present was of delicate texture, almost lanugo-like.

There was no abnormality of the sweat mechanism, such as is found in so-called hereditary ectodermal dysplasias.[1]

The urine was normal, the Kahn reaction of the blood was negative and the basal metabolic rate was —1 per cent. A blood count showed 5,900 leukocytes, and a differential count showed 63 per cent polymorphonuclear leukocytes and 29 per cent lymphocytes. Chemical examination of the blood showed cholesterol 184 mg. per hundred cubic centimeters. The results of a dextrose tolerance test were as follows (amount per hundred cubic centimeters of urine): fasting, 80.1 mg.; one-half hour, 148.3 mg.; one hour, 108.3 mg.; one and one-half hours, 190.9 mg.; two hours, 93.0 mg.

All tests of the urine for sugar gave negative results.

The patient's course in the hospital was characterized by a prompt subsidence of the pyogenic element of the finger tips within eight days with routine local therapy. At the time of his discharge, four weeks after admission, much of the sensitiveness had disappeared from the finger tips along with regression of the deep fissures. The soldier was able to continue on duty during the next month. When he was seen again at the end of this time his finger nails were yellow-white, brittle, still half the normal expected length and partly detached except for the extreme base protected by the cuticle. The exposed portion of the nail bed was still covered by the hyperkeratotic and slightly desquamating cutaneous surface, and the finger tips remained thickened and slightly cracked but not fissured. The only complaint at this time was pain on movement of the nails incident to the handling of objects.

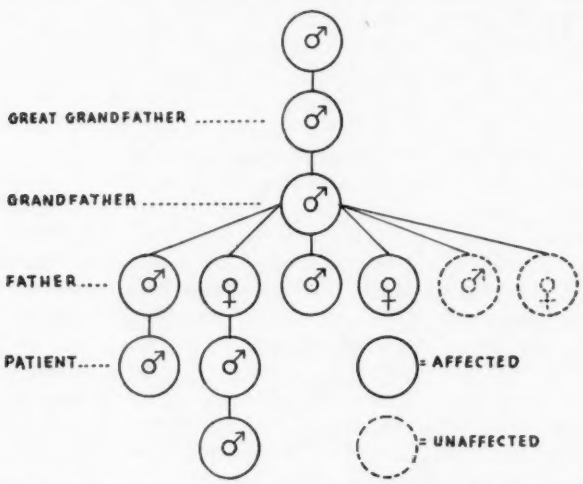
The family history is of greatest interest in this case, although there is unfortunately no available information as to the siblings of the first, second and third generations to be involved. Whether the children of the father's siblings were affected or not and the degree of variation in severity in the persons known to have the condition are not known. However, only 2 persons besides the patient were known to have associated involvement of the hair. The accompanying chart indicates the descent through six generations with the male predominance of the dystrophy over the female (8 cases to 2).

Benedek [2] in a recent comprehensive survey of the literature has commented on the scarcity of reports in reference to simultaneous dystrophy

1. Sutton, R. L., and Sutton, R. L., Jr.: Diseases of the Skin, ed. 10, St. Louis, C. V. Mosby Company, 1939, pp. 561 and 1427. Lowenburg, H., Jr., and Grimes, E. L.: Ectodermal Dysplasia of the Anhidrotic Type, Am. J. Dis. Child. **63**:357-365 (Feb.) 1942.

2. Benedek, T.: Hereditary Dystrophy of the Hair and Nails, J. Invest. Dermat. **4**:285-293 (Aug.) 1941.

of the hair and nails and in particular of cases in which all the nails were involved. He recorded the fourth case of dystrophy of the nails of the fingers accompanied by onychia. Our case is therefore believed to be the fifth and is of further interest in that the patient was of Slavic descent, whereas most of the patients reported on have been of French or German ancestry. Our case does not fit into that group [3] in which hypothyroidism or large thyroid strumas [4] are present, nor have we evidence to suggest [5] that the involvement increased in severity with successive generations. It would appear that the defect in this particular family resembled the majority of the other series in presenting features of a mendelian dominant trait. The associated onychias in our case were evidently not as severe as in the cases reported by Benedek, and



Descent of dystrophy of the hair and nails through six generations.

hospitalization and appropriate therapy afforded rather prompt relief. The factors responsible for this complication as previously indicated were undoubtedly unavoidable exposure, trauma and difficulty in maintaining good personal hygiene of the hands.

SUMMARY

1. We have observed another case of congenital dystrophy of the nails and hair involving all the nails, and the hair of the scalp, axillas and groin.

3. Barrett, A. M.: Hereditary Occurrence of Hypothyroidism with Dystrophy of Hair and Nails, Arch. Neurol. & Psychiat. **2**:628-637 (Dec.) 1919.

4. Hoffman, F.: Ueber Verkümmerung der Augenbrauen und der Nägel bei Thyreoidosen, Arch. f. Dermat. u. Syph. **89**:381, 1908.

5. Walter, A. L., and Bradford, W. L.: Congenital Familial Atrophy of the Nails, J. Missouri M. A. **25**:20-22 (Jan.) 1928.

2. We have noted the male predominance of this defect in six generations and a Slavic rather than a French or Teutonic racial background.

3. We have reported the fifth case of this disease associated with onychia of the fingers (misjudged trichophytosis on first medical observation).

4. These defects observed in an otherwise able-bodied man of military age constituted a definite physical handicap not sufficiently severe to disqualify him for army service but of a degree necessitating limitation of his duties.

TIME FACTOR IN IRRADIATION

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This and subsequent communications comprise a study of the factors which influence the biologic activity of radiation. The present paper deals with an explanation of the influence of the time factor on the response of tissue to measured quantities of radiation. The reaction medium has been the human skin in vivo, and the roentgen rays used were of low voltage and either unfiltered or slightly filtered.

The biologic response of living substances to measured quantities of roentgen rays and gamma rays is recognized by many as depending on the intensity rate. The accepted meaning of the term intensity rate implies the quantity of radiation delivered in a unit of time and is expressed as roentgens divided by the time in which they are applied, or roentgen per minute.

Probably the first published definite relation between biologic response and intensity rate was that of Holthusen in 1933.[1] He gave a curve showing the number of roentgens required to produce uniform erythemas, with variations in intensity rate ranging from 500 to 0.5 r per minute. According to this curve, shown in figure 1, equivalent effects on the skin are produced with 500 roentgen minutes of the high intensity rate radiation and with 2,300 roentgen minutes of the low intensity rate radiation.

Several investigators failed to confirm the existence of such a relation. Sievert and Forssberg,[2] operating with high intensity rates, of from 24,000 to 7,800 r per minute, gave doses of 165 r to drosophila eggs but failed to find any dependence of the biologic response on the intensity

This research was made possible by a grant from the Lillia Babbitt Hyde Foundation.

From the Skin and Cancer Unit of the New York Post-Graduate Medical School and Hospital.

1. Holthusen, H.: Vergleichende Untersuchungen über die Wirkung von Röntgen- und Radiumstrahlen, Strahlentherapie **46**:273-288, 1933.

2. Sievert, R. M., and Forssberg, A.: The Time Factor in the Biological Action of Roentgen Rays: III. Investigations at Very Short Irradiation Times, Acta radiol. **17**:290-298, 1936.

rate. Kirchhoff and Kelbling,[3] using rabbits' testicles as reaction material, obtained negative results with varied intensities. Timoféeff-Ressovsky and Zimmer [4] found that the rate of mutation of drosophila as affected by radiation is independent of the intensity rate and proportional only to the quantity of radiation. The latter two reaction materials, however, are known to possess little recovering power, and because of this any pronounced difference in results should not be expected. With the radiation intensities employed by Sievert and Forssberg the change of intensity rate is small and in that region of the curve where the change of biologic response is smallest. These negative results reported, therefore, are to be expected.

Other investigators, who used more suitable test materials and low intensity radiation, obtained results which are fully in agreement with

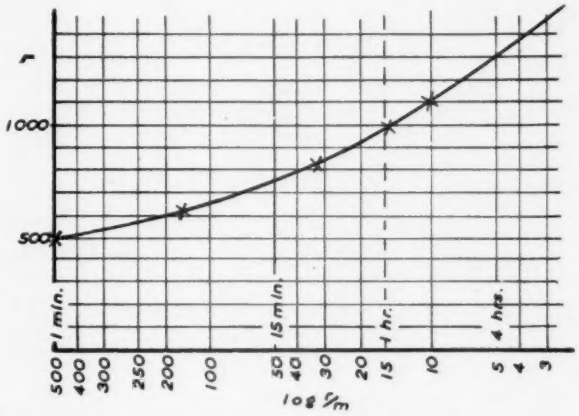

Fig. 1.—This figure is an illustration of Holthusen's curve, and the crosses represent results of experimental determinations performed on living human skin. Our figures agree perfectly with those of Holthusen. This curve shows the number of roentgens required to produce equal cutaneous reactions with various radiation intensities.

the Holthusen curve. Gregori [5] with drosophila eggs, Miescher [6] with rabbits' ears and Reisner [7] with human skin found that biologic changes

3. Kirchhoff, H., and Kelbling, W.: Experimenteller Beitrag zum Zeitfaktorproblem, Strahlentherapie **60**:444-467, 1937.

4. Timoféeff-Ressovsky, N. W., and Zimmer, K. G.: Strahlengenetische Zeitfaktorversuche an Drosophila melanogaster, Strahlentherapie **53**:134-138, 1935.

5. Gregori, A.: Die biologische Wirkung der kontinuirlichen und rhythmisch unterbrochenen Röntgenbestrahlung auf die Eier von Drosophila melanogaster, Strahlentherapie **60**:422-426, 1937.

6. Miescher, G.: Tierexperimentelle Untersuchungen über den Einfluss der Fraktionierung auf den Späteffekt, Acta radiol. **16**:25-38, 1935.

7. Reisner, A.: Hauterythem und Röntgenstrahlung, Ergebn. d. med. Strahlenforsch. **6**:1-60, 1933.

depend on the intensity rate of the irradiation. The experimental results of MacComb and Quimby [8] also agree, and curve 11 of Meyer [9] is an experimental verification of the Holthusen curve.

Thus, any failures to disclose a dependence of biologic response on intensity rate can now be explained, and the Holthusen curve might be accepted as substantially correct. But the entire problem of recovery of living substances from radiation injury depends so much on the exact quantitative relation of these factors that a redetermination of these relations under carefully controlled conditions is highly desirable. Much of the criticism against the Holthusen curve was directed to the fact that the portion of the curve obtained with the low intensity rate was determined with radioactive substances. It is therefore implied that the quality factor of the radiation was not well controlled.

The present investigation was carried out with nonfiltered radiation of low voltage, mainly for the reason that with this quality radiation more easily readable cutaneous reactions are obtained. Particular attention was directed toward maintaining the quality factor constant, but other factors also were kept constant.

The intensity rate is often linked to a rate of injury or to the vigorousness of an assault caused by the radiation on living tissue. It is postulated that a low injury rate may cause little or no biologic injury but that higher rates of injury caused rapidly increasing and greater damage to living substances. The terms intensity rate and exposure time, however, are physically definitely linked, one being inversely related to the other.

The recovery or healing of tissue from an injury is known to depend on time.[10] Therefore a recovery or healing following radiation injury can with justification be assumed to depend on time. An attempt is made to interpret the lesser effectiveness of radiation applied at a low intensity rate as against the greater effectiveness of equal quantities of radiation delivered at a higher intensity rate on the basis that healing takes place even during the application of the radiation to the living substances. This has been reported by Mutscheller [11] as derived by calculation from existing biologic and experimental data. Thus, during

8. MacComb, W. S., and Quimby, E. H.: The Rate of Recovery of Human Skin from the Effects of Hard or Soft Roentgen Rays or Gamma Rays, Radiology **27**:196-207, 1936.

9. Meyer, W. H.: The Co-Relation of Physical and Clinical Data in Radiation Therapy, Radiology **32**:23-45, 1939.

10. Lecomte du Noüy, P.: Cicatrization of Wounds: II. Mathematical Expression of the Curve Representing Cicatrization, J. Exper. Med. **24**:451-460, 1916.

11. Mutscheller, A.: Recovery Function of Irradiated Tissues: Theoretical and Experimental Study, Radiology **38**:53-73, 1942.

long exposure times with low intensity rates more healing can be assumed to take place than during shorter exposure times with high intensity rates.

EXPERIMENTS

The experimental procedure was planned with the aim of obtaining the most highly accurate and dependable results possible with cutaneous reactions. This is best accomplished by exposing with no appreciable loss of time two adjacent areas on the skin of the same person. One variable factor can then be adjusted so that equal reactions or tints on the skin indicate equality of the biologic results. For example, if an exposure from one distance in a certain length of time produces the same tint as another exposure on a nearby area at double the distance and in four times the exposure time, then there would be an indication of no recovery or repair.[12] If, however, at the greater distance more than four times the exposure time is required to obtain equal tints, then the excess over this can be taken as a measure of the extent of recovery. Therefore, while a large number of exposures on the skin had to be made to obtain two producing exactly equal tints on the two adjoining areas, only those actually giving equal tints were usable for a point on the curve. Numerous exposures were necessary in the first series, because there were no generally accepted data to guide us. It was therefore necessary to resort to the trial and error method. For the second series of experiments fewer exposures sufficed. Figure 2 is a photograph of two areas showing equality of tint. The upper had 435 r at 435 r per minute, and the lower had 835 r at 15.2 r per minute.

To obtain five points on a curve ranging from 435 to 12.1 r per minute in intensity or from exposure times of one minute to seventy-five minutes, 23 persons were exposed to 52 kilovolts of nonfiltered radiation. In the second series 100 kilovolts of nonfiltered radiation was employed. Only 6 persons were exposed in order to obtain identical tints for the five points.

Every subject received first a dose of radiation which was uniform in every detail. This quantity of radiation was sufficient to produce a visible erythema. To a contiguous area immediately after the application of the first dose was administered a quantity of radiation with a different intensity but sufficient to produce the same degree of erythema as in the first test area. With this method, differences in sensitivity and also differences in exposure to light, air, friction, changes in temperature, etc., were the same in both experimental areas. Therefore, whatever

12. Exposing a small area (1 inch [2.5 cm.] squared) from great distances (10 to 35 inches [25 to 89 cm.]) does not cause any change in absorption in a thin layer such as the skin. Any possible changes are theoretically unimportant or practically not measurable.

changes took place in the test area also took place in the others and the relation between the two was not affected.

All the exposures in the first series were made with 52 kilovolts and 10 milliamperes. There was no filtration except the inherent filtration The radiation had a half value layer of 0.5 mm. of aluminum. The second series were made with 100 kilovolts, 5 milliamperes and no filter. The half value layer was 0.8 mm of aluminum. The number of roentgens delivered per minute was practically the same in the two series.

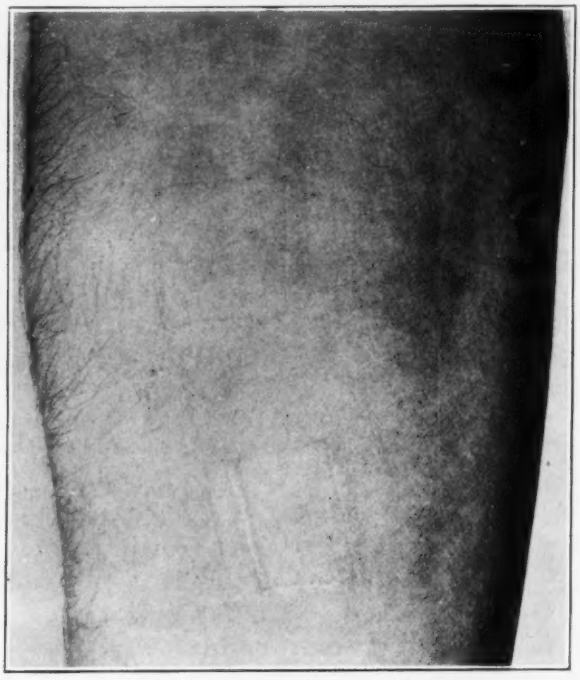

Fig. 2.—Equal cutaneous reactions from radiations applied at different intensity rates with 100 kilovolts. The upper area received 435 r (Wulf) in one minute, and the lower area received 835 r (Wulf) in fifty-five minutes.

The variable factors in addition to the slight changes in quality in the two series were distance and time.

The actual experiments were carried out by exposing either the inner surface of the forearm or the inner surface of the thigh of each of a group of young and middle-aged white persons of both sexes with various complexions. The radiation was applied perpendicularly to an area of skin 1 inch square, and the surrounding skin was protected with lead foil.

Since the x-ray tube is located in a closed metallic housing surrounded with oil and thus the exact location of the focal spot on the

anode cannot be reached for measuring the exact distance, we employed an indirect triangulation method to measure the skin-target distance. It consisted of making a roentgenogram of a strip of lead of known length and distance from the film. From the length of the shadow, the length of the lead strip and its known distance from the film, the skin-target distance for each of the various distances employed was calculated.

The observations of the cutaneous reactions were made both in daylight and in artificial light. The reactions were artificially increased by slight rubbing or applying warm moisture uniformly over both areas. In case of close equality of tints, observations were repeated independently by several observers.

In the accompanying table the intensity rates of the radiation at the skin expressed in roentgens per minute are stated in the third column; in the fourth column are given the exposure times required for the

The Exposure Times for Equal Cutaneous Reactions with Equal Nonfiltered Radiations *

Patient No.		Intensity,				Comparative		
52 Kv. Series	100 Kv. Series	r per Min.	Exposure, Min.	r per Erythema	Ratio, r per Erythema	Holthusen Values	Log (r/m)	Log r_t-r_1
Each	Each	435	1′	435†	1.00	500	2.64	2.57
79	84	127	4′20″	550	1.26	630	2.10	2.70
80	76	34.7	20′	695	1.60	800	1.50	2.83
66	81	15.2	55′	835	1.92	960	1.15	2.92
68	..	12.1	75′	910	2.12	1,040	1.07	2.96

* An oil-immersed x-ray tube with no filters was used.
† Instead of 300 r, as normally required for a threshold erythema, 435 r was administered so as to obtain a definite and unquestionable erythema reaction.

erythemas of the same degree with the highest intensity, which is that stated in the first line, and any other smaller intensity. The fifth column contains the number of roentgens required for an erythema reaction equal to that produced by the highest intensity, and the ratio in roentgens required is given in the sixth column. The figures in the fifth column are multiplied by 1.15 to make them comparable with those of the Holthusen curve, and these values, listed in the seventh column, are plotted as crosses in figure 1, which is the original Holthusen curve. These crosses therefore are experimentally determined erythema values obtained both with 52 and with 100 kilovolt nonfiltered radiation.

The agreement of these results obtained experimentally with nonfiltered radiation with the Holthusen curve is such that over the range considered the validity of the Holthusen curve is confirmed once again.

COMMENT

The physical measure of radiation quantity is generally expressed as the product of radiation intensity (I) or roentgens per minute and

exposure time (t). Thus, the radiation quantity (S) is given by the formula $I\ t = S$ or $I = \frac{S}{t}$

This formula makes it possible to compare biologic results either with intensity or with exposure time [13] while keeping the other factor constant.

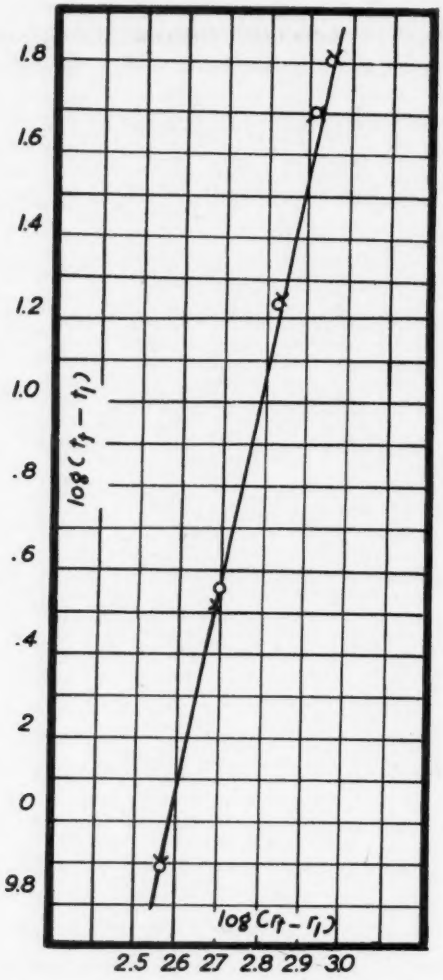

Fig. 3.—Logarithmic plot of the experimental data, showing as a straight line and indicating that the larger number of roentgens required for equal cutaneous reactions at low intensity is due to recovery during the time of the irradiation.

Dependence on maximum results for intensity is found in many photochemical reactions, but the process of recovery of living substances from

13. Mutscheller, A.: The Bunsen-Roscoe Law in Irradiation, Proc. Soc. Exper. Biol. & Med., to be published.

radiation injury is definitely a process depending on time.[10] Thus one is led to assume that healing or recovery takes place both during and after the exposure to radiation.

It is further evident from well conducted experiments that for the lethal injury of a cell generally a multiple of hits by photons are required. Therefore there is first a latent radiation quantity to be administered before any cells are destroyed. This latent dose for human skin is roughly 130 roentgen minutes.[11]

With reactions of this type one can plot the experimental data which produce equal quantitative results (S) as log r/m (r/m indicating roentgens per minute) and as log $(r_t - r_l)$,[14] as is done in figure 3. The striking fact revealed is that the graphs for both series are straight lines and both have the slope of about 0.22. This fact may justify the following construction:

$$\log r/m = k \ (\log [r_t - r_l]).$$

This definition of radiation quantity is complied with if from the total exposure time (r_t) the value of the latent radiation dose (r_l) is subtracted. Also, it is thereby confirmed that a time factor of healing or recovery of cells from radiation injury is revealed by these experimental findings. This is in agreement with previously obtained results.[11]

SUMMARY AND CONCLUSIONS

The shape and bend of the curve of the experimental data obtained under the conditions outlined are such that the Holthusen curve in the roentgen ray range used, i. e. between 435 and 12.1 r per minute, is confirmed and found to be substantially correct.

In more specific terms, these conclusions are for unfiltered radiations of 52 and 100 kilovolts or a half value layer in aluminum of 0.50 and 0.80 mm. respectively.

Casual connection between total radiation quantities applied and either the intensity rate or the exposure time minus a latent radiation quantity is pointed out.

Reasons are given why the decrease of "effectiveness" of radiation with lower intensities in reality is due to healing or recovery during the irradiation.

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14. Steinmetz, C. P.: Engineering Mathematics, ed. 3, New York, McGraw-Hill Book Company, 1917.

HISTIOCYTOMA CUTIS: A VARIANT OF XANTHOMA

HISTOLOGIC AND CLINICAL STUDIES OF TWENTY-SEVEN LESIONS IN TWENTY-THREE CASES

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Dermatologists are generally agreed that there exists a cutaneous entity which has been variously known as fibroma simplex (Unna, 1896), nodulus cutaneus (Arning and Lewandowsky, 1911), dermatofibroma lenticulare (Schreus, 1930), histiocytoma cutis (Woringer, 1931, and Senear and Caro, 1936), dermatofibroma (Traub and Monash, 1932) and nodular subepidermal fibrosis (Michelson, 1933). The appearance of the firm, pink to tan, slightly elevated, usually single, slowly growing nodules is characteristic and is familiar enough to require no elaboration here; the histologic features with ordinary stains are likewise relatively constant (with occasional exceptions), easily recognized and well known. A recent review by Sweitzer and Winer [1] summarized all this material concisely and well.

There are, however, two unsolved problems in connection with this lesion. The first is its seeming rarity in some parts of the country. One of us (H. L. A.) encountered but 1 recognized instance of it during more than three years in the department of dermatology of the University Hospital in Ann Arbor, Mich., while in private (group) practice in Honolulu, 23 cases have been observed in less than three years. It is likely, of course, that this discrepancy is due largely to extrinsic or irrelevant factors and that it is apparent rather than real; however, it certainly exists, and our own is by no means the only discoverable example of it.

HISTORICAL BACKGROUND

The other unsolved problem which in part occasions this report is the controversy emphasized by Senear and Caro [2] in 1936 regarding the

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Read at the staff meeting of The Clinic, August 1942.

From the departments of dermatology and clinical pathology, The Clinic.

1. Sweitzer, S. E., and Winer, L. H.: Fibrotic Nodules of the Skin, Arch. Dermat. & Syph. **45**:315 (Feb.) 1942.

2. Senear, F. E., and Caro, M. R.: Histiocytoma Cutis, Arch. Dermat. & Syph. **33**:209 (Feb.) 1936.

pathogenesis and histologic nature of this lesion. They confirmed previous studies by Woringer [3] and other dermatologists of the French school, in which it had been shown that many of the lesions of this disease contained phagocytosed fat. In the 15 of their 25 cases in which stains for fat were made the lesions were all found to contain intracellular lipids. In 5 cases (including 3 of the remaining 10) these authors demonstrated the ability of the tumor cells to phagocytose, after the fashion of reticuloendothelial cells everywhere, particles of iron previously injected in their vicinity in the form of a 10 per cent solution of saccharated ferric oxide. Their conclusion was that most of these tumors were not primarily fibromas but localized aggregates of reticuloendothelial cells, and they followed the example of the French writers in calling them histiocytomas.

Stecker and Robinson [4] in 1941 reported 62 cases in which the clinical diagnosis was dermatofibroma and studies with special stains were made for elastic tissue and nerve elements but not, oddly enough, for fat. Notwithstanding this omission, they concluded that the histiocytes observed by Senear and Caro had merely "wandered into" the lesions and that the tumors were really fibromas. Sweitzer and Winer [1] have more recently reported their failure to find "any excessive presence of fat" in these lesions; they did not define what they meant by "excessive," though it would seem that any intracellular fat might be regarded as excessive in a fibroblast.

FIBROBLASTS VERSUS HISTIOCYTES

The statement that fibroblasts should not be expected to contain fat is made despite much opinion to the contrary. Weidman and his associates [5] have repeatedly stated that young, actively growing fibrous tissue cells are prone to "undergo xanthic change." This concept, however, seems open to an alternative interpretation. Maximow and Bloom [6] expressed the opinion that the fibroblast is a highly specialized cell, incapable, unlike the multipotent tissue histiocyte, of changing its structure and function under most types of stimulus. The histiocyte (reticulo-

3. (*a*) Woringer, F.: Histiocytoma of the Leg, Bull. Soc. franç. de dermat. et syph. **38**:1401, 1931. (*b*) Civatte, cited by Senear and Caro.[2]

4. Stecker, J. F., and Robinson, W. L.: Dermatofibroma, Arch. Dermat. & Syph. **43**:498 (March) 1941.

5. Weidman, F. D., and Boston, L. N.: Generalized Xanthoma Tuberosum with Xanthomatous Changes in Fresh Scars of Intercurrent Zoster: Adenocarcinoma of Ampulla of Vater at Necropsy, Arch. Int. Med. **59**:793 (May) 1937. Weidman, F. D., and others: Xanthoma and Other Dyslipoidoses, Philadelphia, University of Pennsylvania Press, 1941.

6. Maximow, A. A., and Bloom, W.: A Text-Book of Histology, ed. 1, Philadelphia, W. B. Saunders Company, 1930, p. 142.

endothelial cell) is, on the contrary, highly labile and readily becomes ameboid and actively phagocytic under many types of inflammatory stimulation.

It is not generally realized that these two types of cell are normally present in the subcutaneous tissues in approximately equal numbers. In active inflammation, particularly subsiding processes, they both proliferate, the histiocytes becoming the ameboid, phagocytic polyblasts of the inflammatory reaction and the fibroblasts eventually forming the scar by laying down collagen fibrils. It is important to recognize that these two cellular systems, so different in function, cannot be distinguished by ordinary histologic methods. They can be sharply separated only by vital staining with colloidal dyes; the histiocytes actively ingest the particles of dye, while the fibroblasts take no part in this function. The fibroblasts similarly maintain their identity in tissue cultures and remain highly differentiated elements of constant appearance and function which are unable to take and store particles from weak solutions of colloidal dyes. This statement, of course, is relative. Maximow emphasized that in tissue cultures subjected to sufficiently high concentrations of colloidal dyes the fibroblasts as well as the histiocytes eventually become filled with particles of dye, but the process in the case of the fibroblasts is a relatively passive one.

The ubiquitous nature of the foam cell and the process by which it arises is reflected in the wide variety of conditions, apart from xanthoma, in which it is found. We have regularly observed foam cells in chronic, nonspecific inflammatory processes of all kinds and have often seen, with the aid of stains for fat, various transition stages between the typical foam cell and the typical spindle cell. The reticuloendothelial component of the so-called fibroblastic granulation tissue of perirectal fistulas and infected pilonidal sinuses can be outlined by stains for fat, while routine hematoxylin and eosin stains fail singularly to differentiate the two systems. In chronic specific granulomas the reticuloendothelial cells are characteristically perpendicularly arranged at the periphery of the lesions, and these cells, likewise, often contain intracellular lipids, unrecognizable by ordinary stains. It thus appears likely that the precursor of the foam cell of xanthoma is the histiocyte rather than the fibroblast and that there is no necessity to assume that the fibroblast ever contains intracellular lipids except under the most extraordinary conditions of exposure to such substances.

It is important to realize, however, that neither Senear and Caro nor the French dermatologists to whose reports they referred have regarded all tumors corresponding to the *clinical* entity under discussion as being *histologically* identical. They have all admitted the existence of true fibromas of the skin. Their thesis has been, in general, that the majority

of the tumors previously regarded on histologic grounds as fibromas are in fact composed primarily not of fibroblasts producing new collagen but of histiocytes invading old damaged collagen. Only Civatte [3b] suggested a possible reconciliation of the two views, in that the histiocyte might be regarded as the parent cell of the fibroblast and that histiocytomas might therefore be regarded, in a sense, as fibromas arrested in an early stage of development.

Proponents of the fibroblastic view have been as a rule less generous; they have for the most part taken the stand that the clinical entity is a histologic entity and that the tumors are fibrous and not histiocytic. Hamilton Montgomery appears to be almost the only American dermatologic writer since Senear to accept the histiocytoma as an entity. He regards it, much as do Senear and Caro, as either a xanthic sort of tumor or a tumorous sort of xanthoma.[7] He has emphasized, indeed, that it may not be possible to differentiate histologically between histiocytoma and the "solitary fibrous stage of xanthoma." Lest this statement be taken to mean that histiocytoma is merely the solitary fibrous stage of xanthoma, it should be noted that in no previously reported cases, and in no instance in our own series, was there the slightest suggestion of the clinical appearance of xanthoma.

In the American literature Lewis and Sachs [8] and Bernstein,[9] besides Montgomery, have used the name histiocytoma to designate this sort of tumor; but the name has so far failed of general acceptance. It is largely for this reason that the following 23 cases are being reported and analyzed.

SUMMARY OF CASES

Table 1 gives most of the pertinent facts with regard to the cases; slightly more detail is given for 4 of them, to indicate the sort of problems clinically presented and the increasing ease with which the clinical diagnosis of histiocytoma came to be made.

CASE 20.—A white woman aged 45, had multiple hard pink pigmented slightly raised subcutaneous nodules, not increasing in size, on the right ankle (two), calf (one) and left arm (two), one present for "years" and the others for less than a year. Two were excised for histologic examination. Sarcoid and Kaposi's sarcoma were considered in making a diagnosis.

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7. Montgomery, H.: Xanthomatosis: A Systemic Disease, Proc. Staff Meet., Mayo Clin. **12**:640 (Oct. 13) 1937; Cutaneous Xanthomatosis, Ann Int. Med. **13**:671 (Oct.) 1939. Montgomery, H., and Osterberg, A. E.: Xanthomatosis, Arch. Dermat. & Syph. **37**:373 (March) 1938.

8. Lewis, G. M., and Sachs, W.: Lipoidal Histiocytoma (Fibroxanthoma): Report of a Case, Ann. Int. Med. **9**:1746 (June) 1936.

9. Bernstein, J. C.: Hemosiderin Histiocytoma, Arch. Dermat. & Syph. **40**:390 (Sept.) 1939.

TABLE 1.—*Clinical Analysis of Twenty-Three Cases of Histiocytoma Cutis*

No.	Name	Age	Sex	Race	Previous Injury	Duration	Physician Consulted	Clinical Diagnosis	Growing ?	Lipid Content	Diabetes Mellitus ?	Urinary Sugar ?	Blood Pressure	Comment
1	FNJ	15	M	ptH *	Yes	4 mo.	Surgeon	None	Yes	Abundant	Grandfather	.....	.....	Recurrence in site, 4 months later
2	EH	16	F	.....	....	15 mo.	Surgeon	None	....	.....	.....	.....	.....	
3	MP	14	M	White	No	4 mo.	Surgeon	Histiocytoma	No	Patchy	No	None	.....	
4	ELK	25	F	White	....	2 yr.	Gynecologist	Histiocytoma	No	Central	.....	None	160/100	Obesity
5	HYL	43	F	Chinese	No	3 yr.	Surgeon	Wart	Yes	Patchy	1st cousin	None	162/ 90†	Obesity
6	BF	33	F	ptH *	No	5 yr.	Gynecologist	Histiocytoma	Yes	None	3d cousin	None	160/100	Obesity
7	THL	29	F	Chinese	No	3 yr.	Gynecologist	.....	Yes	None	No	None	Normal	
8	CH	31	F	White	No	"Years"	Dermatologist ‡	Histiocytoma	No	.....	Grandmother	None	Normal	
9	JTW	..	F	White	...	.....	Dermatologist ‡	Histiocytoma	....	None	.....	None	Low	
10	AM	..	F	White	...	.....	Surgeon	None	....	Patchy	.....	.....	.....	
11	CS	28	F	White	No	"Years"	Gynecologist	Histiocytoma	No	Loaded	No	None	Normal	
12	MR	41	F	White	No	1 yr.	Surgeon	None	Yes	None	No	.....	Low	Two more lesions a year later, 1 a histiocytoma
13	LSC	29	F	White	No	2 yr.	Internist	None	Yes	Scanty	No	None	Normal	
14	OWG	..	F	White	....	"Years"	Surgeon	None	....	Loaded	.....	None	Normal	
15	EC	25	F	White	Yes	2 yr.	Surgeon	Histiocytoma	No	None	Mother	None	Normal	
16	WHE	46	F	White	No	6 mo.	Surgeon	Histiocytoma	No	Scanty	Son	None	160/ 90	
17	CDM	48	F	White	No	1 yr.	Dermatologist ‡	None	No	.....	Mother	None	150/100	
18	C	43	F	White	No	1 yr.	Gynecologist	None	No	Abundant	Mother	None	Normal	
19	DA	..	M	Japanese	....	.....	Surgeon	Wart	....	Abundant	.....	None	Normal	
20	WM	45	F	White	No	"Years"	Dermatologist	None	No	.....	No	None	170/100	Five lesions, 2 excised
21	GM	38	M	Japanese	No	5 yr.	Dermatologist	Histiocytoma	No	Present	No	.....	.....	
22	KB	55	F	ptH *	Yes	4 yr.	Gynecologist	Histiocytoma	No	Loaded	No	None	230/130	Obesity
23	NRD	33	F	White	No	1 wk.	Surgeon	Histiocytoma	No	Moderate	2 sisters	None	.....	
	EPT	28	F	White	No	7 yr.	Dermatologist	Histiocytoma	No	None	No	.....	.....	Fibroma histologically
	ERA	35	M	White	Yes	3 mo.	Dermatologist	Histiocytoma	No	Peripheral	No	.....	.....	Resolving "abscess" from intradermal injection of typhoid vaccine

* ptH indicates part Hawaiian.

† Definitely hypertensive level for the patient's race (Chinese).

‡ The patient consulted a dermatologist because of an unrelated dermatosis; the histiocytoma was an incidental finding.

CASE 6.—A part Hawaiian woman aged 33 had a slowly growing firm pigmented subcutaneous tumor in her right flank. It was located at her waistband and could not be diagnosed clinically. It was probably a histiocytoma. Excision was advised.

CASE 13.—A white woman aged 29, had a circular firm slightly raised pink nodule, 5 mm. in diameter, with 1 mm. pigmented areola, present about two years, on the left shin. It was probably a histiocytoma. Excision was advised.

CASE 15.—A white woman aged 25, had a histiocytoma removed from the inner part of the right thigh.

AGE, RACE AND SEX INCIDENCE

Age appeared to be a factor of no great significance; it varied in our series from 14 to 55 years. Nor was race distribution remarkable; there were 2 Japanese, 2 Chinese, 3 part Hawaiian and 16 white patients. This distribution is comparable to the total distribution in our practice of lesions of such relatively slight seriousness. With more serious or unmanageable conditions the proportion of Japanese patients increases somewhat. As to sex distribution, in ours as in previously reported series, the lesions occurred predominantly in females. We have felt that this striking disproportion (19 to 4) may be due at least in part to the fact that men are likely to regard such small, indolent and painless lesions as too trivial to warrant medical attention.

PREVIOUS TRAUMA

The question of preexisting lesions or previous trauma was answered in the negative by 14 and in the affirmative by 3 patients. One patient (case 1) had scratched his arm playing football four months before, and within a week or two a tumor had developed at the site of the injury, which rapidly grew to a diameter of nearly 1 cm. This lesion proved to be loaded with lipid; it was still growing at the time of removal. There was a family history of diabetes mellitus (in a grandfather). One year later an exactly similar nodule was removed from the same site and was found likewise to be loaded with intracellular lipid material.

The second patient (case 15) recalled having repeatedly traumatized a "whitehead" on her thigh some two years before, which subsequently developed into the tumor for which she sought medical advice. This lesion contained no lipid histologically; however, in this case there was also a family history of diabetes mellitus, in the patient's mother. The lesion had grown no larger for some time prior to its removal.

The third patient (case 22) gave a history of previous trauma, with a highly circumstantial story of a needle which had been "sat on and

lost" six years before and which had reappeared through the skin two years later at the exact site, on the side of one thigh, in which the tumor made its appearance shortly afterward. This tumor contained abundant lipid material; it was not growing larger at the time of removal, and there was no family history of diabetes, though the patient herself had hypertension.

DURATION OF LESIONS

The duration of the lesions at the time of removal varied so widely as to be without apparent significance. Three lesions were said to be of less than four months' standing; in 1 of these lipids were abundant, and in the other 2 they were patchy and scanty. Four were reported to have been present for "many" years; 2 of these proved to be loaded with lipid, and on the other 2 stains for lipid were not done. The average age of the 12 lesions thought to be stationary in size at the time of removal was two and eight-tenths years (assuming "many" to

TABLE 2.—*Relation of Family History of Diabetes Mellitus to Lipid Content of Tumors in Fourteen Cases of Histiocytoma*

Family History	Lipid Content of Lesions		
	Abundant	No or Scanty	Not Known
Diabetes	3	3	2
No diabetes	2	6	1
Not asked	2	3	1

mean "five" years); the average age of the 6 lesions believed to be growing larger at the time of removal was only one and eight-tenths years, with a maximum of three years.

RELATION TO DIABETES MELLITUS AND HYPERTENSION

The question of a family history of diabetes mellitus or other metabolic disorders was put to 17 patients; 8 of these gave a history of diabetes mellitus in a close relative (mother in 3, a grandparent in 2 and a son, a first cousin and 2 sisters in 1 each). The ratio of diabetic family history to no diabetic family history for the patients whose lesions contained abundant lipid was 3 to 3 (with 2 unascertained); the ratio for the patients whose lesions contained no, or only slight, lipid was considerably lower: 2 with to 6 without such a history (and 4 uncertain). One patient in addition to the 8 reported a remote relative (a third cousin) with diabetes (table 2).

Urinalyses were made in all the cases of histiocytoma except 5, and in many of the cases they had been made repeatedly over a period of several years and in our own laboratory. In no case had glycosuria been demonstrated at any time. In the cases in which there was a diabetic

family history, urinalysis was omitted in only 1 instance. Dextrose tolerance tests were not made in any case, nor were any determinations of blood sugar or cholesterol level made.

Determinations of blood pressure were made or had been made (on several occasions in most instances) in 17 cases. In 7 of these the average pressure was abnormally high (table 1). Three of the 7 were in the group with a diabetic family history (table 3).

GROWTH OF LESIONS

The histiocytoma was believed by the patient to be growing larger at the time it was excised in 6 cases; in 12 cases it was believed not to

TABLE 3.—*Relation of Blood Pressure Level to Family History of Diabetes Mellitus in Fourteen Cases of Histiocytoma*

Blood Pressure	Diabetic Family History		
	No	Yes	Not Known
High	3	3	1
Normal or low	4	3	3
Not taken	2	2	2

TABLE 4.—*Relation of Growth Status of Lesion to Lipid Content in Fifteen Cases of Histiocytoma*

Status of Lesion	Lipid Content of Lesions		
	Abundant	No or Scanty	Not Known
Growing larger	1	5	0
Not growing	4	5	3
Not asked	2	2	1

be increasing in size. It was believed to be growing larger in only 1 of the 5 cases in which abundant lipid was found and this question asked, whereas of 10 patients with scanty or no lipid who were asked this question, 5 believed the tumor was growing and 5 stated that it was not (table 4).

Only one recurrence after simple surgical excision (case 1) was observed. In 1 patient (case 12) two additional tumors developed in different locations a year after the first one was excised, only 1 of which was a histiocytoma. Two patients (cases 14 and 20) had multiple tumors, 1 having two and the other five (two excised).

LOCATION OF TUMORS

The extremities were the site of the lesions in 18 cases and the trunk in the remaining 5. We feel that the relative frequency of minor trauma to the extremities may have a bearing on this disproportion, the case histories to the contrary notwithstanding.

PATIENTS' CHOICE OF PHYSICIAN

In 11 instances the patient consulted a surgeon in our group regarding the lesion, in 6 instances a gynecologist and in only 5 instances a dermatologist. In the last-mentioned 5 the histiocytoma was the reason for the visit in only 2 cases. In every case the patient had previously been a patient at The Clinic; thus in no instance did the lesion prompt an initial visit, and in only one twelfth of the cases was the dermatologist selected and consulted because of the lesion. These figures contribute, we feel, to a clearer understanding of the general impression that the lesion is comparatively rare.

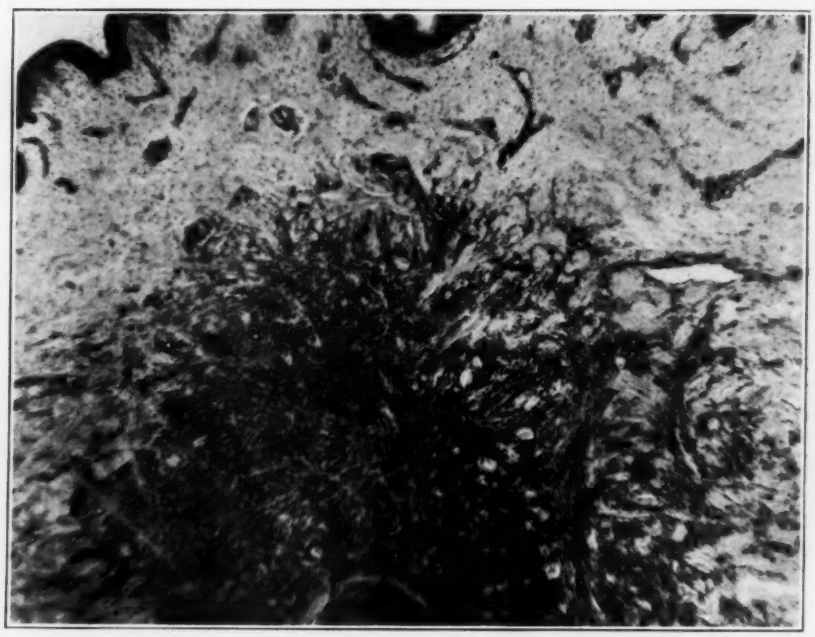

Fig. 1 (case 17).—Lesion, 3 mm. in diameter, located almost 1 mm. beneath the epidermis. The histologic features are typical of the smaller, more deeply located lesions (hematoxylin and eosin, × 78).

HISTOLOGIC STUDIES

The twenty-seven tumors studied varied in diameter from 2 to 10 mm. and were round or oval in shape. They were confined to the corium, approximately one-half occurring in the papillary portion immediately adjoining the basal cell layer of the epidermis and the remainder deeper, separated from the epidermis by 0.5 mm. or more of normal tissue (fig. 1). The epidermis showed reactive changes, the extent of which depended on the size of the lesion and its location in the corium, the larger and more superficially located lesions giving

rise to the greatest changes. Acanthosis, of moderate degree, was observed most frequently and was often associated with slight hyperkeratosis. The epidermis covering several of the larger tumors was thinned and atrophic, with absence of the rete pegs. In only 7 of the 27 lesions was the epidermis entirely normal, and all of these were 1 mm. or more beneath the surface.

All of the tumors were clearly circumscribed but not sharply so; they had no capsule and merged gradually at the periphery into normal

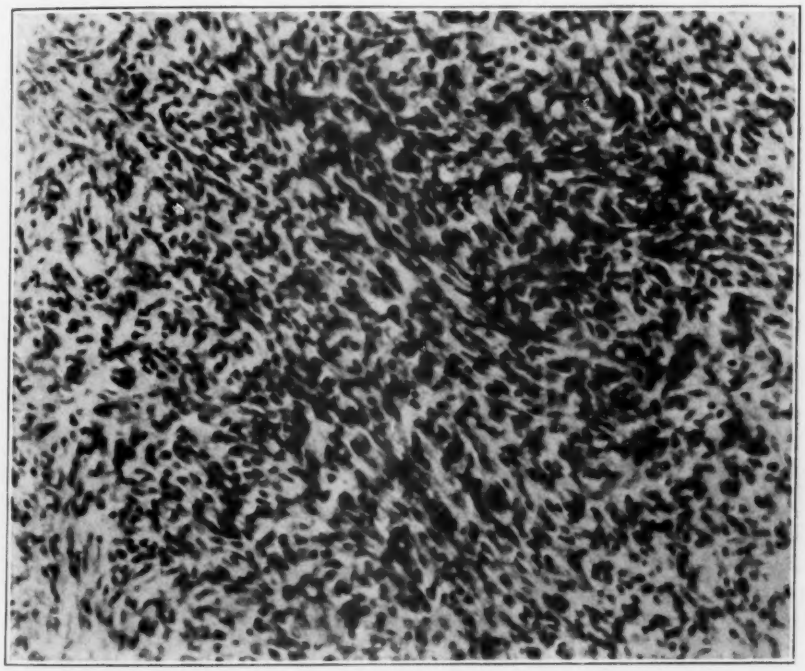

Fig. 2 (case 1).—Spindle cells in the first lesion, which contained abundant lipid (fig. 6; hematoxylin and eosin, × 260).

dermal structure. They were characteristically composed of inextricably mingled interlacing spindle cells with large, pale-staining, round or oval nuclei. Stained by hematoxylin and eosin the cells indeed resembled fibroblasts. The smaller lesions were fibrous in appearance; the larger ones (over 5 mm. in diameter) were more highly cellular, simulating fibroma, myoma and even fibrosarcoma (fig. 2). Mitoses, however, even in the large and highly cellular tumors, were uniformly lacking.

Three were indistinguishable histologically from fibroxanthoma of tendon sheath origin, and all of these contained small, poorly formed giant cells, with centrally arranged nuclei, which were loaded with

lipid. A few typical foam cells (fig. 3) were also found in 1 of these (case 19). Many of the cells in the larger tumors exhibited a vacuolated cytoplasm suggesting an approach to foam cells, although they still retained their large nuclei and elongated shapes (fig. 4).

An almost constant feature was the presence of perivascular lymphocytes and thickened arterioles at the periphery of the tumors. Even the large, cellular, sarcoma-like nodules invariably contained a sprinkling of lymphocytes and plasma cells, diffusely arranged. Sweat glands were occasionally found within the lesion, relatively unchanged although surrounded by the usual interlacing spindle cells.

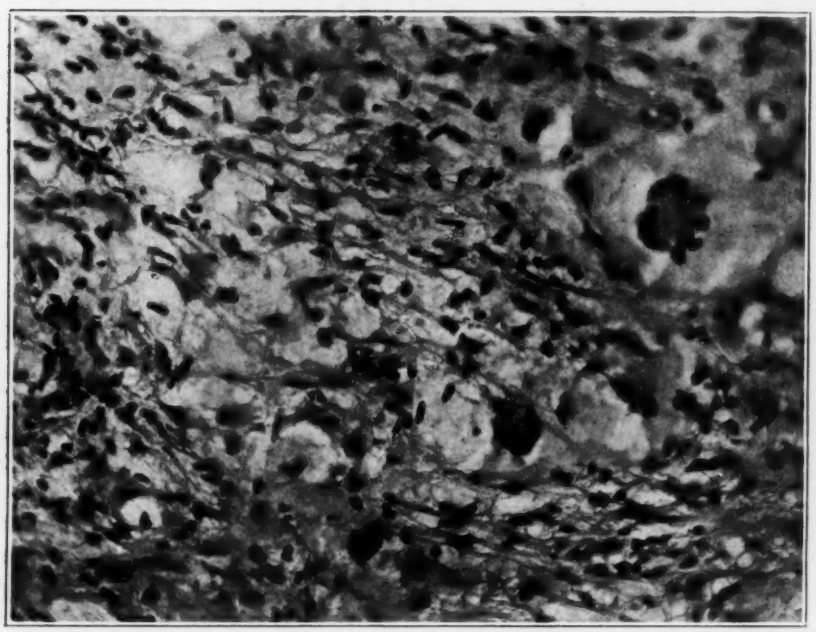

Fig. 3 (case 19).—Typical foam cells and a Touton giant cell in the lesion. These histologic features are characteristic of xanthoma; in our series only one tumor presented this appearance. (Hematoxylin and eosin, × 533.)

One tumor (patient EPT, table 1), diagnosed clinically as a typical histiocytoma, presented an unexpected histologic picture (fig. 5). It was 5 mm. in diameter and was located immediately beneath the epidermis. It was sharply demarcated at the periphery and was composed of stellate cells which were remarkably uniform in size and shape and separated by thick bundles of collagen. The jumbled, irregularly interlacing spindle cells characteristic of the other nodules were completely lacking. This tumor was thought to be a true fibroma. Yet from the clinical standpoint it was one of the most typical "histiocytomas" of the entire series.

Stains for collagen by a modified Cajal trichrome technic were made on 22 of the 27 tumors. The appearance of the collagen varied with the size of the tumor. In the large lesions (over 5 mm. in diameter) the normal collagen bundles were sharply broken up at the periphery and none were found within the lesion. The smaller tumors contained collagen in the form of fine strands and bundles, some of which gave altered staining reactions suggesting degenerative changes. All stages from the fragmentation and degeneration to the complete disappearance of dermal collagen could be traced from the smaller to the larger lesions.

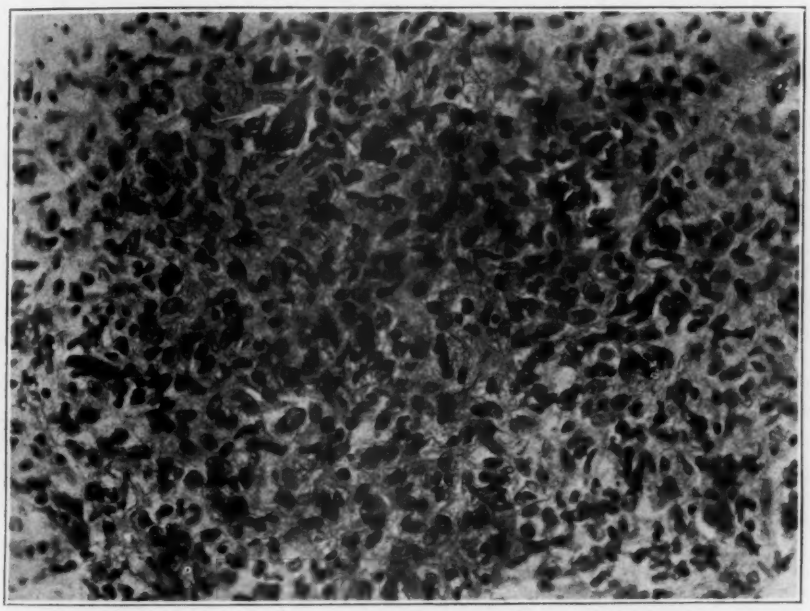

Fig. 4 (case 11).—Lesion showing vacuolated cytoplasm morphologically approaching that of a foam cell (hematoxylin and eosin, × 548).

Stains for elastic tissue were made on 17 tumors. These showed that elastic fibrils, like collagen bundles, were entirely absent in the larger tumors and present only in the form of fine strands and fragments in the smaller ones.

Sudan III and hematoxylin stains were made on 22 tumors, and intracellular lipids were demonstrated in 15 of them in the form of fine droplets. The amount varied with the size of the tumor; in general, the smaller lesions contained relatively small amounts of fat or none at all, while the 7 larger tumors (over 5 mm. in diameter) were all packed with sudanophilic lipid droplets (fig. 6). One tumor (case 4), though only 2 mm. in diameter, contained abundant lipid material in its exact center, while the cells at its periphery contained none. One relatively acellular, deeply located, fibrous-looking nodule (case 18), only 3 mm.

in diameter, contained abundant lipid, while several slightly larger lesions contained none.

POLARISCOPIC STUDIES

An improvised polarizing microscope was made by simply inserting polaroid disks, with their optical axes at right angles to one another, below and above the stage of a microscope. This procedure yielded an

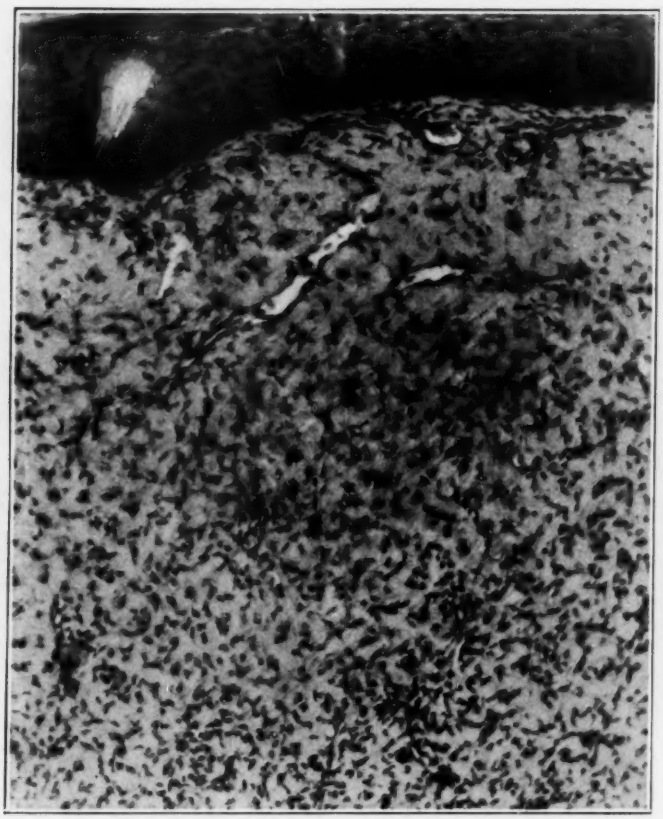

Fig. 5.—Lesion from patient EPT (table). Note stellate cells and uniformity of picture. No lipid was found. This was regarded as a true fibroma (hematoxylin and eosin, × 260).

almost perfectly dark field except in areas in which the polarized light from the lower polaroid disk passed through material which rotated it even slightly out of the plane of polarization; such rotation permitted it to pass relatively freely through the second disk and caused the material which had made it rotate to appear brightly illuminated. Subsequent observations made with a mineralogist's polarizing microscope employing regular Nicol prisms and a rotating stage gave exactly the same results with somewhat greater brilliance.

Unstained frozen sections of 19 lesions from 17 cases were examined by this method, and photorotatory crystals were demonstrated inside the lesion in 6 of them. It was noted, when the rotating stage of the polarizing microscope was used, that nearly all of the slender, needle-shaped crystals "extinguished" (i. e., disappeared as a result of their failure to rotate the plane-polarized light incident on them from below) whenever their long axis was turned into the same plane as that light or at right angles to it, that is, at both "90 degree" positions (fig. 7). A small number of crystals "extinguished" at an angle of about 23 degrees from the 90 degree axes (note that 23 is roughly one fourth

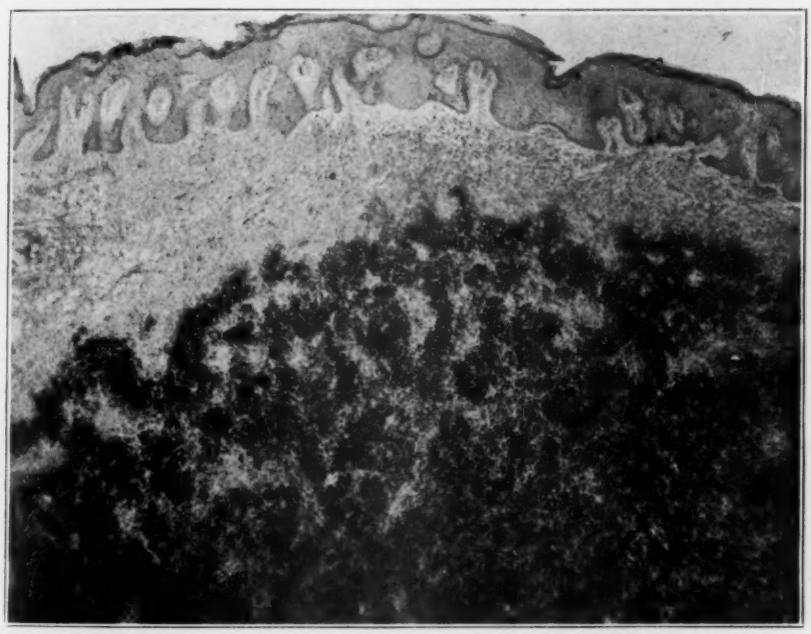

Fig. 6 (case 1).—First lesion (fig. 2). The lipid appears black in this photograph. This appearance is fairly typical of all tumors in our series over 5 mm. in diameter (sudan III and hematoxylin, × 76).

of 90), and a much smaller number of crystals manifested this phenomenon at angles varying from 19 to 40 degrees. This phenomenon can be explained, apparently, on the basis of the usual behavior of either monoclinic or triclinic crystal forms with relation to polarized light. It does not appear that it bears any regular relation to the phenomenon of rotation of the plane of polarized light by substances in solution. All that was shown, therefore, was the presence of crystals in the sections manifesting this phenomenon. In all instances these crystals were also visible by unpolarized light of reduced intensity, although only the larger ones could be seen in that way. In only 1 instance (case 21)

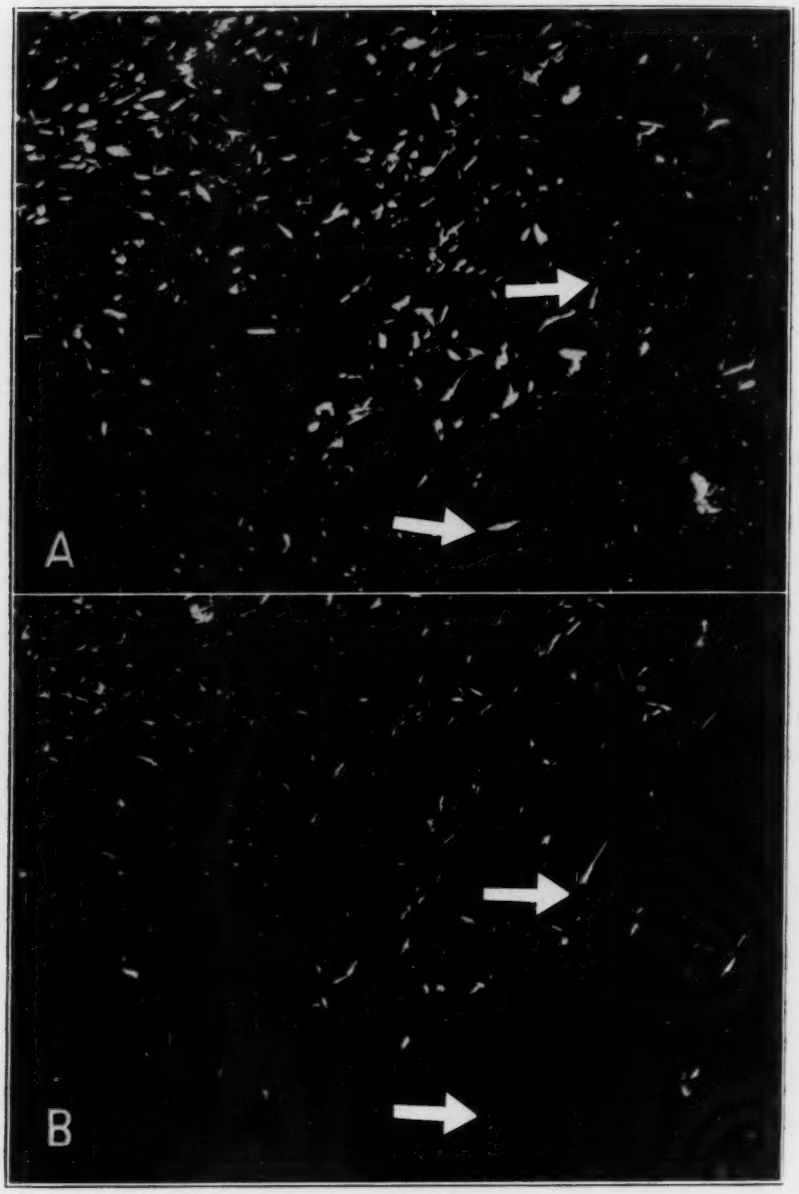

Fig. 7 (case 21).—Unstained frozen section viewed with improvised polarizing microscope (× 260). In *B* both lower and upper polaroid disks were rotated approximately 23 degrees clockwise from the position they occupied in *A*, with the result that many crystals visible in *A* have been "extinguished" (lower arrows) and vice versa (upper arrows). Note also failure of aggregate in lower right hand corner to extinguish completely because of nonuniform orientation of the tiny crystals composing it. Sudan III stain showed abundant lipid.

was a crystal suggestive of the crystalline pattern of cholesterol observed. It was visible by ordinary light and manifested the same rotatory effect as did the needle-shaped crystals when viewed by polarized light.

The results of this study are summarized in table 5. Seven lesions which contained only slight to moderate amounts of lipid material as shown by sudan III stain failed to exhibit crystals when examined by polarized light. One lesion (case 19) which was loaded with lipid also showed no crystals when this examination was made. It is thus apparent that this technic is not a sensitive method of demonstrating tissue lipids. It appears to depend on the presence of crystals, and there is no regular correlation between the presence of these and the presence of fat. In general, however, crystals are much more likely to be found in large

TABLE 5.—*Relation of Lipid Content of Lesions as Shown by Sudan III Stain to Presence of Refractile Crystals as Shown by the Polarizing Microscope*

Case and Lesion	Lipid Material with Sudan III	Refractile Crystals with Polarized Light
1 (b)	4 plus	4 plus
3	1 plus	Negative
4	2 plus	2 plus
5	1 plus	Negative
6	Negative	Negative
7	Negative	Negative
10	1 plus	Negative
11	4 plus	4 plus
12 (a)	Negative	Negative
(b)	1 plus	Negative
14 (a)	4 plus	4 plus
(b)	Negative	Negative
15	Negative	Negative
16	1 plus	Negative
18	3 plus	2 plus
19	4 plus	Negative
21	4 plus	4 plus
22	3 plus	Negative
23	1 plus	Negative

lesions with abundant lipid than in lesions which contain relatively little fat (table 5).

The picture produced by polarized light is extremely interesting. In some of the tumors the crystals were minute, appearing as fine points of light; in others they were in the form of long, slender, sharp-pointed needles; and in still others they were in the form of amorphous-looking aggregates. A possible relationship of the histologic appearance of a given lesion to its crystal pattern as determined by polarized light and to its cholesterol, cholesterol ester and neutral fat content is under investigation at present.

COMMENT

We believe it is a mistake to consider all subepidermal nodules belonging to the clinical entity under discussion as members of the same pathologic entity. Although clinically similar, they may differ entirely in causation, histogenesis and morbid anatomy. As a case in point,

patient ERA (table 1) had a subepidermal nodule on the flexor surface of the forearm which followed an intradermal inoculation with typhoid vaccine. It increased slowly in size to a diameter of about 8 mm. and when first observed by us, three months after the inoculation, was a typical example of histiocytoma. Microscopic examination, however, revealed a resolving abscess surrounded by a rim of lipid-filled reticuloendothelial cells, giant cells of the foreign body type and lymphocytes. The majority of the nodules in our series, however, certainly appeared not to be fibromas in the true oncologic sense of that word. Only one lesion (patient EPT, table 1) fulfilled the histologic criteria usually accepted for a true benign connective tissue neoplasm of fibroblastic origin.

The essential cell, at least in the majority of the tumors in our series, appears to be the histiocyte rather than the fibroblast. This statement is made advisedly. It is based on: (1) the moderate to high intracellular fat content in 15 of the 22 tumors on which stains for fat were made and the decreased and degenerated collagen in all of these, as well as in the remaining 7, on which stains for collagen were made; (2) the presence of giant cells in 4 tumors; (3) the presence of a vacuolated cytoplasm in the cells of many of the larger tumors, suggesting a morphologic approach to foam cells, and (4) typical foam cells in 1 lesion. It is apparent that all of these observations point toward xanthoma and away from fibroma. Yet the typical histologic picture of xanthoma was not observed in a single case, and in no instance was xanthoma clinically suggested.

Accordingly the designation "histiocytoma" seems appropriate, although we are not inclined to view the lesion as an actual neoplasm, since it is by no means certain that it is not frequently initiated by some sort of trauma and since there appears to be a definite, presumably intrinsic upper limit on its growth. The almost constant presence of lymphocytes and thickened arterioles in the lesions in our series also points to an inflammatory cause. In this respect our views coincide with those of Michelson.[10] However, we are convinced of the histiocytic nature of most of the tumors and prefer to think of them as variants, or perhaps even as transitional forms, of xanthoma. We recognize the possibility, however, of a relatively high fibroblastic content in some of the lesions, particularly those in which stains for fat give negative results; and there is undoubtedly some fibroblastic proliferation in all of them.

The remarkably high incidence (nearly 50 per cent) of a history of diabetes mellitus in a close relative certainly invites the suggestion

10. Michelson, H. E.: Nodular Subepidermal Fibrosis, Arch. Dermat. & Syph. **27**:812 (May) 1933.

that patients with histiocytomas have in common a tendency to abnormal metabolism of fat or carbohydrate or both. Perhaps this is more often true when the lesions are full of lipid than when they are not (table 2). Possibly it is permissible to regard histiocytomas as an expression of local repair processes rendered abnormal by some factor affecting the fat metabolism, and thereby the behavior of histiocytes, somewhat as keloids may be regarded as an expression of repair processes disturbed by some factor affecting the behavior of fibroblasts.

SUMMARY

Histiocytoma cutis has long been regarded by most students of dermal pathology (with the exception of the French school and, in America, Senear and Caro and Montgomery) as the result of localized fibroblastic proliferation.

The incidence of cases of this tumor in dermatologic practice shows extraordinary disparity between different parts of the United States and even between different dermatologists in the same locality.

Women outnumbered men by nearly 5 to 1 in our series of cases; age and race, however, did not appear to be significant etiologic factors.

Trauma appeared to be a definite etiologic factor in only 3 out of 17 patients questioned regarding it.

A family history of diabetes mellitus in a close relative was obtained from 8 of 17 patients questioned. Three of these 8 had moderate hypertension; 3 did not. None of the 8 had glycosuria.

Intracellular lipid material was demonstrated in 15 of 22 tumors (in 13 of 18 cases) on which stains for fat were made.

Stains for collagen on 22 tumors showed collagen to be entirely lacking within the lesion in 8, present only in fine strands in 10 (with the normal bundles ending abruptly at the margin of the lesion) and broken up to some extent in 4. In no case was it either undisturbed or increased.

Typical foam cells were found in only 1 lesion. Many of the cells in 7 lesions, from 6 patients, however, possessed a vacuolated cytoplasm suggesting a morphologic approach to the foam cells of xanthoma, and lipid material was abundant in all 7.

Giant cells approximating the Touton type were found in 4 tumors (3 cases, with 1 recurrence). They were in every instance associated with atypical vacuolated cells suggestive of xanthoma and with a high fat content of the lesion. In all lesions showing vacuolated cells and giant cells, the resemblance to "fibroxanthoma" of tendon sheaths was striking.

Perivascular round cell infiltration and thickening of arterioles near the periphery of the tumors was a striking feature in almost every case

and was present to some degree in every lesion except the single typical fibroma observed, in which it was altogether lacking.

The correct diagnosis was made in 13 of the 23 cases before sections were seen; in 8 no diagnosis was made, and in 2 the lesion was seen by a surgeon only and was merely referred to loosely as a "wart." The reliability of the diagnostic criteria and the relative importance of index of suspicion are both high, however, and the correct diagnosis in cases observed during the past year and a half has been made in nearly every instance by the surgeon or gynecologist who first saw the lesion.

Simple surgical excision is the treatment of choice; nonintervention, as suggested by Sutton and Sutton,[11] is equally satisfactory from the standpoint of the tumor but less satisfactory from the standpoint of the average patient's psychologic reaction and the academic advantages of histologic study, including the diagnosis, which cannot of course be established otherwise.

CONCLUSIONS

Histiocytoma cutis (Woringer and Senear and Caro) is a tumor resulting from sharply localized proliferation of cells (1) which have the ability, and usually the opportunity, to phagocytose lipids or other foreign materials and are therefore of reticuloendothelial origin and (2) which invade, damage and displace the normal dermal collagen instead of producing new collagen.

Histiocytoma cutis is therefore related to the xanthoma group and not to the fibromas and, like xanthoma, is probably related in some way to the type of metabolic disorder observed in diabetes mellitus.

The seeming rarity of histiocytoma cutis appears to be attributable in part at least to the fact that it is not often complained of by a patient and that when it is complained of a dermatologist is not likely to be selected for the consultation.

The correct diagnosis may be made with a high degree of accuracy on clinical grounds alone, though differentiation from fibroma (aside from the statistical improbability of any given lesion's ever being a fibroma) and from other still less common miscellaneous lesions requires histologic study as well.

As suggested by Senear and Caro, these lesions should provide an excellent field, in other than private office practice, for the investigation of the behavior of cells of the reticuloendothelial system. Their clinical importance, aside from the apparent connection with diabetes mellitus and possibly with hypertension, appears to be slight, indeed.

W. O. Clark, geologist in the Hawaii Sugar Planters' Association Experiment Station, assisted in the preparation of the section dealing with the polariscopic studies.

11. Sutton, R. L., and Sutton, R. L., Jr.: Diseases of the Skin, ed. 10, St. Louis, C. V. Mosby Company, 1939, p. 647.

CI. HISTOCHEMISTRY OF PEMPHIGUS LESIONS

WITH SPECIAL REFERENCE TO BULLOUS FORMATION

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AND

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ST. LOUIS

In this investigation, the problem of pemphigus was approached by a study of certain physiochemical and histochemical factors concerned in the production and properties of the characteristic lesion of this disease, a blister.[1] Attempts were made to induce formation of artificial blisters in pemphigus skin by injection of fluids under pressure. The cohesive property of unaffected skin from patients with pemphigus was estimated by the use of measured weights, and the proteins of blister fluids were studied polarographically. Finally, the tissue minerals of unaffected pemphigus skin and of lesions were investigated by microincineration and spectrographic analysis. Cantharides blisters and areas showing Nikolsky's sign were also studied histochemically. Thus, an attempt was made to correlate various factors in the developmental stages of blister formation.

The clinical picture of pemphigus is striking, being characterized by insidious or rapid onset, usually in an adult, of bullous or vesicobullous formations on the skin and mucous membranes, particularly the buccal and nasal mucosa. Associated constitutional symptoms may be mild or extremely severe. The course may be persistently progressive or remissions may occur, but the disease is frequently fatal. The remark by Ormsby [2] that "The problem (of pemphigus) is not yet entirely settled" seems to be an understatement of the situation, for the term pemphigus is little better than the old catchall "eczema." It seems logical to con-

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Drs. M. F. Engman Sr. and E. V. Cowdry suggested this study.

Studies, observations and reports from the Barnard Free Skin and Cancer Hospital and the Anatomical Laboratory, Washington University School of Medicine.

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1. Defined as a circumscribed accumulation of fluid. A blister is called a bulla if it is larger than 0.5 cm. in diameter, and a vesicle if it is smaller.

2. Ormsby, O. S.: Diseases of the Skin, Philadelphia, Lea & Febiger, 1937.

sider pemphigus vulgaris as a heterogeneous group of diseases rather than a separate clinical entity. Similarly, pemphigus foliaceus and pemphigus vegetans are probably diseases involving and originating from multiple factors.

The literature on pemphigus is confusing. Gawalowski [3] stated the belief that bullae form due to acute lymphatic edema which is brought on by the action of epinephrine, and Talbott, Lever and Consolazio [4] seem to have demonstrated changes of the adrenal insufficiency type in their metabolic studies. There are reports "proving" that the causative agent is bacterial, a streptobacillus (Bacterium pemphigi) [5] or a streptococcus.[6] Many investigators, including Grace,[7] have expressed the belief that bacteria when found represent only a terminal change. Filtrable viruses have been reported [8] to be the cause of pemphigus, although many efforts [9] to confirm this view have been unsuccessful. Most of the recent investigators agree that the blister fluid is sterile and, by the methods employed, indistinguishable from serum transudate.

Many methods of treatment have been advocated, but no specific remedy or routine has been found. In 1923 Davis and Davis [10] reported that with a regimen involving the use of iron cacodylate and a coagulant beneficial results were obtained in 6 of 7 cases of pemphigus. Subsequent papers [11] dealing with the Davis treatment have reported favorable

3. Gawalowski, K.: New Findings in Pemphigus Vulgaris: Preliminary Communication, Arch. Dermat. & Syph. **6**:476 (Oct.) 1922.

4. Talbott, J. H.; Lever, W. F., and Consolazio, W. V.: Metabolic Studies on Patients with Pemphigus, J. Invest. Dermat. **3**:31 (Feb.) 1940.

5. Eberson, F.: Studies on Etiology of Pemphigus: Bacteriologic Findings in Group of Cases of Pemphigus, Arch. Dermat. & Syph. **8**:204 (Aug.) 1923.

6. Welsh, A. L.: Specificity of a Streptococcus Isolated from Patients with Pemphigus, Arch. Dermat. & Syph. **30**:611 (Nov.) 1934.

7. Grace, A. W.: Pemphigus Evidence in Support of a Bacteremia as an Explanation of Certain Terminal Changes in the Blood Picture, Arch. Dermat. & Syph. **30**:22 (July) 1934.

8. Urbach, E., and Wolfram, S.: Virus of Pemphigus and Dermatitis Herpetiformis, Arch. Dermat. & Syph. **33**:788 (May) 1936. Grace, A. W., and Suskind, F. H.: An Agent Transmissible to Mice Obtained During a Study of Pemphigus Vulgaris, Proc. Soc. Exper. Biol. & Med. **37**:324, 1937; An Investigation of the Etiology of Pemphigus Vulgaris: The Isolation of a Transmissible Agent from a Fourth Case of the Disease, J. Invest. Dermat. **2**:1, 1939.

9. Fleck, L., and Goldschlag, F.: Further Experimental Studies on Pemphigus, Brit. J. Dermat. **51**:70, 1939. Markham, F. S., and Engman, M. F., Jr.: An Inquiry into the Cause of Pemphigus: Is It a Virus Disease? Arch. Dermat. & Syph. **41**:78 (Jan.) 1940.

10. Davis, R. H., and Davis, W. D.: A Contribution to the Treatment of Pemphigus, Arch. Dermat. & Syph. **8**:627 (Nov.) 1923.

11. (*a*) Wende, G. W.: Pemphigus: Experience with the Davis Treatment, Arch. Dermat. & Syph. **11**:782 (June) 1925. (*b*) Davis, R. H.: Treatment for Pemphigus: A Further Report, ibid. **19**:451 (March) 1929.

results, but some commentators on these reports [12] stated that under their own management beneficial effects were not always as consistent as Davis and Davis indicated. Grindon [13] used the Davis treatment but replaced the iron cacodylate with tryparsamide. Schamberg [14] used colonic irrigations and intramuscularly administered arsenic. Several authors [15] have reported favorably on the use of germanin but have emphasized its toxicity. The intramuscular use of mercury bichloride has been proposed.[16] Then with the era of vitamins and sulfanilamide it was natural that these should be tried. Sulfanilamide has been reported to have been used successfully.[17] Concentrated viosterol brought about improvement in 8 of 9 cases reported by Tauber and Clarke.[18] A "cure" with riboflavin was announced by Topping and Knoefel,[19] while Wolf and Lewis [20] reported a failure after using riboflavin supplemented with smallpox vaccine. Recently treatment with dihydrotachysterol [21] has been reported to give promising results.

It seems important that experimental work be directed toward the segregation of the specific entities from the heterogeneous group of pemphigoid diseases and then treatments be devised for each entity. Such work has been started with the interesting studies of Talbott, Lever and Consolazio,[4] in which they have segregated acute pemphigus by

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12. Wile, Morrow, Fox, Highman, Schamberg and Irvine, in discussion on Wende.[11a] Wile, U. J., in discussion on Davis.[11b]

13. Grindon, J.: Tryparsamide in Acute Pemphigus, Arch. Dermat. & Syph. **21**:25 (Jan.) 1930.

14. Schamberg, J. F.: Pemphigus Recovery Following Long Continued Colonic Irrigations and Arsenic by Mouth, Arch. Dermat. & Syph. **25**:134 (Jan.) 1932.

15. Kinnear, J.: Pemphigus: A Review of Seven Cases, Brit. J. Dermat. **50**:236 (May) 1938. Tomlinson, C. C., and Cameron, O. J.: Juvenile Pemphigus, Effects of Germanin in Three Cases, Arch. Dermat. & Syph. **38**:555 (Oct.) 1938.

16. Sonnenberg, E.: Concept of Continuous Treatment of Pemphigus with Mercury Bichloride, Ann. de dermat. et syph. **10**:771, 1939; in Wise, F., and Sulzberger, M. B.: The 1940 Yearbook of Dermatology and Syphilology, Chicago, The Year Book Publishers, Inc., 1941.

17. Caro, M. R.: Pemphigus: Treatment with Sulfanilamide; Preliminary Report, Arch. Dermat. & Syph. **37**:196 (Feb.) 1938. Lain, E. S., and Lamb, J. H.: Treatment of a Pemphigoid Eruption with Sulfanilamide: Report of a Case, ibid. **37**:840 (May) 1938.

18. Tauber, E. B., and Clarke, G. E.: Treatment of Pemphigus with Concentrated Viosterol, Arch. Dermat. & Syph. **40**:82 (July) 1939.

19. Topping, M. C., and Knoefel, A. F.: Use of Vitamin G in Pemphigus: Report of a Case of Pemphigus Vulgaris Treated Successfully with Riboflavin, J. A. M. A. **114**:2102 (May 25) 1940.

20. Wolf, S., and Lewis, G. M.: Pemphigus Vulgaris: Failure of Treatment with Riboflavin and Smallpox Vaccine, J. A. M. A. **116**:2017 (May 3) 1941.

21. Lever, W. F., and Talbott, J. H.: Action of Dihydrotachysterol in Chronic Pemphigus, Arch. Dermat. & Syph. **43**:341 (Feb.) 1941.

characteristic metabolic changes and have proposed a method of treatment definitely beneficial under their administration.

These authors [4] made a study of fluid balance in connection with pemphigus and obtained evidence that there was an increase in volume of plasma, blood and interstitial fluid in all patients with generalized cutaneous lesions. Studies of the blood of patients with acute pemphigus showed abnormal concentrations of certain constituents which were consistent with acute adrenal insufficiency. Kulcher and Alderson,[22] studying the relation of water metabolism to experimental infection of the skin, showed that cutaneous infections were resisted better when the water content of the animals was diminished. McMaster [23] found that fluid injected into skin flowed through open channels after the dermis was sufficiently filled with water, as in pitting edema. McMaster's findings indicate that under normal circumstances the movement of fluid in interstitial tissue does not take place as though in preexisting channels. However, when fluid is injected under pressure spaces are forcibly opened up. The present investigations suggest that in pemphigus a certain degree of saturation might exist, which would probably create open channels and thus induce the formation of bullae.

In an effort to check the findings of Talbott and his co-workers, the blood volumes of 4 of our patients with pemphigus vulgaris were determined according to the method of Gregersen and Stewart,[24] modified by the suggestions of Gilder, Müller and Phillips,[25] who assumed that complete mixing of the dye is accomplished at five minutes after injection. Available fluid volumes were estimated according to the method of Crandall and Anderson,[26] as modified by Gregersen and Stewart.[24] All measurements were made with a Coleman double monochromator spectrophotometer.

Attempts were made to determine total body water by methods successfully carried out by Painter [27] in dogs. In adapting the procedure

22. Kulcher, G. V., and Alderson, H. E.: The Relation of the Water Metabolism to Experimental Skin Infections, Brit. J. Dermat. **48**:477, 1936.

23. McMaster, P. D.: An Inquiry into the Structural Conditions Affecting Fluid Transport in the Interstitial Tissue of the Skin, J. Exper. Med. **74**:9, 1941.

24. Gregersen, M. I., and Stewart, J. D.: Simultaneous Determination of the Plasma Volume with T-1824, and the "Available Fluid" Volume with Sodium Thiocyanate, Am. J. Physiol. **125**:142, 1939.

25. Gilder, H.; Müller, O. H., and Phillips, R. A.: Mixing Time of T-1824 in the Blood, Am. J. Physiol. **129**:362, 1940.

26. Crandall, L. A., Jr., and Anderson, M. X.: Estimation of the State of Hydration of the Body by the Amount of Water Available for the Solution of Sodium Thiocyanate, Am. J. Digest. Dis. & Nutrition **1**:126, 1934.

27. Painter, E. E.: Total Body Water in the Dog, Am. J. Physiol. **129**:744 1940.

for urea to human beings, 20 Gm. of urea was given orally immediately after a specimen of blood was drawn for determination of urea. Subsequent samples were taken at hourly intervals for six to eight hours. The values showed a rapid rise, reaching a peak at about two hours, and then fell at a variable rate. Attempts to extrapolate to zero time were unsuccessful because of the apparent variability of rate of absorption from the gastrointestinal tract; even had this been overcome by intravenous injection of urea, there was a technical error of ± 5 per cent involved in each determination of urea, and since the final determination depended on the difference between two values, the method was simply too inaccurate for practical use.

In line with Painter's use of sulfanilamide for the same purpose, we tried the intravenous injection of sodium sulfathiazole (the sodium salt of 2-[paraaminobenzenesulfonamido]-thiazole) (1 Gm.) and its determination by the method of Bratton and Marshall,[28] using the wavelength 510 millimicrons for spectrophotometric measurements. The use of this drug has the advantages that there is no initial concentration in the blood to double the technical error and that the concentration of the sulfathiazole can be determined spectrometrically. The distribution of sulfathiazole in the body, according to Goodman and Gilman,[29] is approximately the same as that of sulfanilamide with the exception that sulfathiazole does not enter the cerebrospinal fluid. We therefore assumed that it could be used to determine total body water. Gregersen and Painter [29a] attempted to use sulfanilamide and thiocyanate (available fluid volume) simultaneously and found an interference between these two reagents in the formation of the azo dye used in the determination. However, the coupling reagent used by these authors was dimethyl-alphanaphthylamine, whereas with the method we use N(1-naphthyl)-ethylenediamine dihydrochloride is the coupling agent and since this causes no interference simultaneous determinations can be made.

Although Painter obtained satisfactory results in determination of total water with sulfanilamide in dogs and although according to Goodman and Gilman the distribution of sulfathiazole in the body is approximately the same as that of sulfanilamide, nevertheless, reports have appeared which cast some doubt on the basic assumption of the determination. Davis,[30] in studies with four sulfonamide compounds, showed

28. Bratton, C. A., and Marshall, E. K.: A New Coupling Component for Sulfanilamide Determination, J. Biol. Chem. **128**:537, 1939.

29. Goodman, L., and Gilman, A.: The Pharmacological Basis of Therapeutics, New York, The Macmillan Company, 1941, p. 1087.

29a. Gregersen, M. I., and Painter, E. E.: The Spectral Absorption of Sulfanilamide and Its Red Azo Dye, Am. J. Physiol. **123**:83, 1938.

30. Davis, B. D.: Binding of Sulfonamides by Plasma Proteins, Science **95**:78, 1942.

that they formed a complex with the albumin in blood plasma, and it is to be expected that this would affect the distribution of the drug in the body. Hansen,[31] Reinhold, Schwartz, Flippin and Bethlahmy[32] and Strauss, Lowell, Taylor and Finland[33] demonstrated that the sulfonamide drugs which they studied did not distribute themselves equally or in proportion to the water content between plasma and corpuscles and this ratio was different for the different drugs. For examples, we give two of our results on the ratios of the total amount of a sulfonamide compound in erythrocytes to the total amount of the drug in serum:[34]

$$\text{Sulfanilamide:}\quad \frac{\text{Erythrocytes}}{\text{Serum}} = \frac{29.7}{11.6} = 2.56$$

$$\text{Sulfathiazole:}\quad \frac{\text{Erythrocytes}}{\text{Serum}} = \frac{0.27}{1.19} = 0.23$$

If one considers these peculiarities of distribution, it is not surprising that sulfathiazole gave us no reasonable values for total body water. In general we may say that our experiments indicate an increase in available fluid volume, in agreement with the results of Talbott and his associates. Our attempts to determine total fluid were unsuccessful.

MATERIAL

The following study of pemphigus records certain physiochemical and histochemical observations of a total of 8 patients whose symptoms were diagnosed clinically as pemphigus vulgaris. Brief summaries of the case histories follow:

CASE 1.—V. C., a 67 year old white man, had bullous lesions on the body and extremities for one year. There were no lesions on the mucous membranes. Nikolsky's sign could be elicited. Iron cacodylate was not administered.

CASE 2.—E. T., a 61 year old white man, had a generalized vesiculobullous eruption for five months. Nikolsky's sign could be elicited. Iron cacodylate was not administered.

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31. Hansen, L.: The Distribution of Free and Conjugated Sulfanilamide and Sulfapyridine Between Corpuscles and Plasma in both Human and Rabbit Blood, J. Lab. & Clin. Med. **25**:669, 1940.

32. Reinhold, J. G.; Schwartz, L.; Flippin, H. F., and Bethlahmy, S.: Permeability of Red Blood Corpuscles to Sulfathiazole, Proc. Soc. Exper. Biol. & Med. **45**:317, 1940.

33. Strauss, E.; Lowell, F. C.; Taylor, F. H. L., and Finland, M.: Observations on the Absorption, Excretion and Distribution of Sulfanilamide, Sulfapyridine, Sulfathiazole and Sulfamethyazole, Ann. Int. Med. **14**:1360, 1941.

34. Dr. C. Carruthers, of the Barnard Free Skin and Cancer Hospital, performed these determinations.

CASE 3.—L. R., a 56 year old white woman, had generalized bullous lesions of eleven months' duration. There were no lesions on the mucous membranes. Nikolsky's sign could be elicited. Iron cacodylate was not administered.

CASE 4.—M. H., a 71 year old white woman, had vesicles and bullae on the face, extremities, chest, abdomen and back for ten weeks. Nikolsky's sign could be elicited. The patient died of cardiac failure. She had received iron cacodylate.

CASE 5.—E. M., a 58 year old white woman, had generalized vesicles and bullae for six months. Nikolsky's sign could be elicited. Much iron cacodylate had been administered over a long period.

CASE 6.—B. Y., a 46 year old white woman, had a generalized bullous eruption of five months' duration. Nikolsky's sign could be elicited. Iron cacodylate was not administered.

CASE 7.—E. H., a 20 year old Negro, had extensive generalized bullae for nine months. The mucous membranes were involved. Nikolsky's sign could be elicited. Iron cacodylate was administered.

CASE 8.—E. B., a 60 year old white woman, had a generalized bullous eruption of four months' duration. Nikolsky's sign could be elicited. She received iron cacodylate treatment over a three year period.

ATTEMPT TO FORM BULLAE BY INJECTION OF FLUID

Since the skin of patients with pemphigus often shows Nikolsky's sign, it was expected that it would be relatively easy to form a vesicle by injection of Ringer's solution into the skin. An apparatus was arranged so that the pressure produced by raising a leveling bulb could be read on a water manometer, and the flow through a 25 gage needle into the tissue could be observed in a pipet graduated in intervals of 0.01 cc. The needle was inserted as closely as possible to immediately under the basal cell layer of the epidermis, and pressures finally equaling 1,000 mm. of water were found to be ineffectual in moving Ringer's solution into the tissues at any appreciable rate. No vesicle appeared, although the pressures were maintained for two hours. Similarly, when the needle was introduced deeper into the dermis, with care to avoid entrance into the subdermal connective tissue, no appreciable fluid could be introduced with the same pressure. Since the maximum possible for blood pressure in the capillaries of the skin is about 800 mm. of water in hyperemia and 700 mm. in histamine flare,[35] it is doubtful that bullae are formed as a result of capillary hydrostatic pressure acting to separate epidermis from dermis.

To substantiate this conclusion further, no bullae could be detected when a 1 : 1,000 solution of histamine phosphate was pricked into the skin causing wheals. Furthermore, when a 1 : 100,000 solution was con-

35. Landis, E. M.: Micro-Injection Studies of Capillary Blood Pressure in Human Skin, Heart **15**:207, 1929.

tinuously introduced over a period of three hours by a 25 gage needle directly under the epidermis at a rate of 10 cc. per hour, no bullae could be produced.

COHESION OF EPIDERMIS TO DERMIS IN PEMPHIGUS

The observation that in pemphigus the epidermis may be easily displaced, i. e. slipped, on the underlying dermis leads one to believe that the epidermis would be readily pulled loose from the dermis. The following experimentation was carried out to measure the ease of mechanical separation. The tasseled end of a thread was attached to the cutaneous surface with Duco cement, and the epidermis around the edge was cut through to the dermis with a razor blade. Weights were attached gradually to the thread until around 300 Gm. was applied, which caused the cement to give way. As the areas covered were 50 to 70 sq. mm., a pull of around 400 to 600 Gm. per square centimeter was represented. Since the epidermis did not pull loose, it would appear that there is no deficiency in the cohesiveness of the collagen attachment of epidermis to dermis but rather that the defect must be in fixation of the epidermis to the dermis in a spatial sense. Cohesion is good, but slipping of epidermis on dermis is greatly increased in pemphigus. This slipping might be conducive to bullous formation by permitting minute vesicles to move freely so as finally to coalesce to form macroscopic bullae.

POLAROGRAPHIC STUDIES

The protein of fluid from pemphigus bullae was studied by Brdička's polarographic method.[36] This method involves the formation of a complex of protein and cobalt chloride in the presence of an ammonia buffer and the measurement by means of the polarograph of the catalytic action of the complex. This action is proportional to the cystine and cysteine groups available for formation of the complex in the protein, and the number of such thiol groups sufficiently reactive to form the complex may be increased by various agents which denature protein. Brdička [37] has shown that the increase in available thiol groups on denaturation with alkali is relatively small in the serums of many malignant lesions and some inflammatory and febrile conditions as compared with that in normal serums.

Figure 1 shows two polarographic records: to the left, of fluid from a pemphigus bulla, and to the right, of normal serum. On each curve appear four "waves": Co, the cobalt wave; P_1, the first protein wave;

36. Brdička, R.: Polarographische Mikrobestimmung von Cystin und Cystein in Hydrolysaten von einigen Proteinen, Mikrochemie **15**:167, 1934.

37. Brdička, R.: Serologische Untersuchungen mit Hilfe der polarographischen Methode und ihre Bedeutung für die Krebsdiagnostik, Acta, Union internat. contre cancer **3**:13, 1938.

P_2, the second protein wave, and H, the hydrogen wave. The height of a wave is the added vertical height to the highest point on the wave from the preceding high point. Thus the P_1 wave is about seven times as high as P_2. In these two curves the ratio of P_1/P_2 is the same, which indicates that the protein involved is similar in serum and in bullous fluid. In figure 2 the change in height of the protein waves varying with different periods of treatment with alkali is shown. Before alkali treatment the first protein wave is much larger than the second. After alkali treatment for one minute both protein waves are much increased, and after twenty minutes this increase is still greater; however, further treatment leads to a decrease in total height. The gradual increase is due to the progressive denaturation of the protein, and the decrease is due to a loss of protein by precipitation. Figure 3 shows the course of

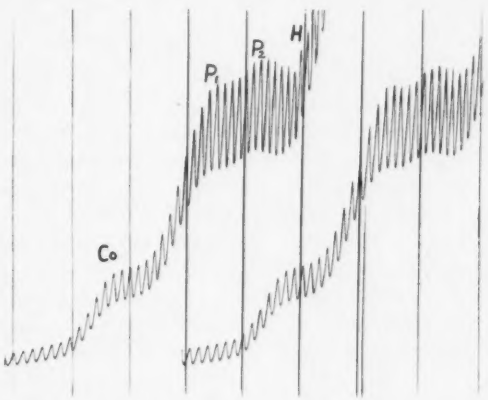

Fig. 1.—Polarograph of fluid from a pemphigus bulla and of serum. The first curve shows the polarograph obtained when 0.02 cc. of the bullous fluid is added to 5 cc. of cobalt test solution, as described under figure 2. The second curve shows the polarograph obtained when serum is substituted. There is no definite difference in the two polarographic curves. The electrolysis was carried out with a saturated calomel half-cell as reference anode connected by agar–potassium chloride salt bridge with the electrolyte. Bridge voltage is 2.0; sensitivity, 0.02; initial applied voltage, — 0.800 to reference; voltage change per abscissa, — 0.200. The instrument used was a Heyrovsky polarograph, Sargent model XI, modified by the addition of an abscissa marker.

denaturation produced by alkali in fluid from a pemphigus bulla. Curve 1, taken after one minute, shows the same ratio of heights of P_1/P_2 as does curve 1, figure 2, for serum. Curve 2 shows the fusion of P_1 and P_2, and curve 3 shows the decrease in total heights. It is unfortunate that the times are not such that curve 2 would have shown the increase in total height of P_1 plus P_2, but this was seen in other cases.

These polarographic studies are as yet inadequate to justify a conclusion, though it appears that the protein of bullous fluid and serum

of patients with pemphigus vulgaris behaves polarographically in the same way as the protein of normal serum. There appear to be no changes such as have been observed in malignant disease.

To determine whether or not the epidermis covering pemphigus bullae is deficient in keratin content, this tissue was studied polar-

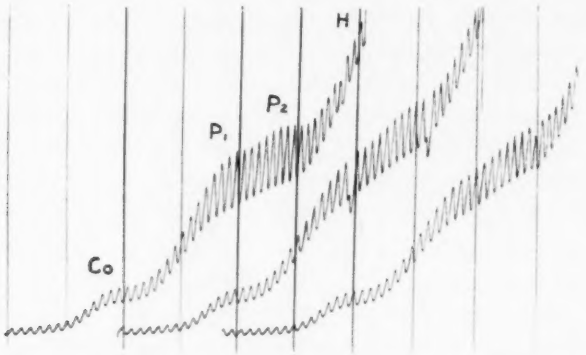

Fig. 2.—Polarograph of serum in the course of denaturation with alkali. The first curve was taken at one minute, the second at twenty minutes and the third at thirty minutes. Waves P_1 and P_2 tend to fuse in curves 2 and 3. For each curve 0.05 cc. of a mixture consisting of 0.2 cc. of serum, 0.2 cc. of water and 0.1 cc. of physiologic solution of sodium hydroxide was added, after the time indicated, to a cobalt test solution consisting of 1 cc. of tenth-molar solution of cobalt chloride, 0.5 cc. of physiologic solution of ammonium chloride, 3 cc. of water and 0.5 cc. of physiologic solution of ammonium hydroxide. The electrolysis was carried out as in figure 1 except that the sensitivity was 0.01.

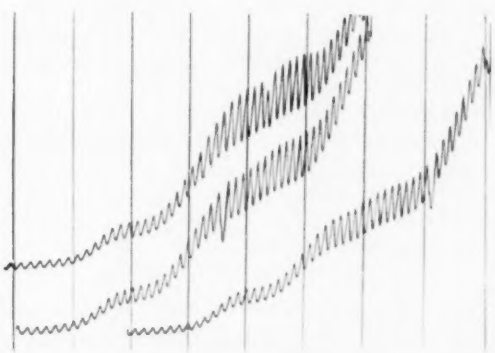

Fig. 3.—Polarograph of fluid from a pemphigus bulla in the course of denaturation with alkali. The quantities of materials used were identical with those described under figure 2. Electrolysis was carried out as described under figure 1. Sensitivity was 0.01. The first curve (the uppermost) was glued on from another polarographic record of the identical electrolysis. Curve 1 was taken after one minute, curve 2 after fifty-five minutes and curve 3 after eighty-five minutes of alkali denaturation.

ographically and compared with normal epidermis. Block [38] has reviewed the literature on keratin, including studies of skin. Several authors [39] have shown that the total cystine content of protein can be determined polarographically if acid hydrolysates of the protein are added to cobalt chloride and properly buffered with ammonium hydroxide and ammonium chloride. Total nitrogen [40] was used as a reference base and the ratio of cystine to total nitrogen observed. No definite difference in this ratio was observable between normal epidermis and the epidermis of pemphigus bullae.

HISTOCHEMICAL STUDIES

Pemphigus Skin.—Histochemistry: The minerals and other biologic constituents of 28 biopsy specimens of affected and of unaffected skin of 8 patients with pemphigus vulgaris were studied histochemically by ordinary histologic technics and by microincineration and spectrographic analysis. In 4 cases specimens were obtained in both the early and the late stage of the disease. Specimens of vesicles of various sizes, from microscopic vacuoles to macroscopic blisters, were obtained in many instances from the same patient. The distribution of these specimens is listed as follows:

Total number of cases of pemphigus	8
Total number of biopsy specimens	28
Active lesions	22
Vesicles	22
Bullae	8
Unaffected skin	6

Comparisons were made with 83 specimens of normal skin taken from as many normal persons and with 55 specimens of pathologic skin from 13 patients with other cutaneous diseases. The distribution of these specimens may be found in a previous publication by MacCardle, Engman and Engman.[41]

38. Block, R. J.: Comparative Biochemistry of the Proteins, in Cold Spring Harbor Symposia on Quantitative Biology, Cold Spring Harbor, L. I., New York, The Biological Laboratory, 1938, vol. 6, p. 79.

39. Brdička, R.: Polarographic Studies with the Dropping Mercury Kathode: The Microdetermination of Cysteine and Cystine in the Hydrolysates of Proteins, and the Course of the Protein Decomposition, Collect. Czechoslov. Chem. Commun. **5**:238, 1933; footnote 36. Sladek, J., and Lipschutz, M.: Polarographic Studies with the Dropping Mercury Kathode: Specific Effects of Some Amino-Acids, Collect. Czechoslov. Chem. Commun. **6**:487, 1934. Stern, A.; Beach, E. F., and Macy, I. G.: Polarographic Microdetermination of Cystine in Protein Hydrolysates, J. Biol. Chem. **130**:733, 1939.

40. Mr. L. Wicks, of the Barnard Free Skin and Cancer Hospital, carried out the hydrolyses and made total nitrogen determinations.

41. MacCardle, R. C.; Engman, M. F., Jr., and Engman, M. F.: Histology of Neurodermatitis, Arch. Dermat. & Syph. **44**:161 (Aug.) 1941.

Specimens of pemphigus skin for biopsy were obtained by scalpel excision with the use of local procaine hydrochloride anesthesia, care being taken to avoid infiltration of the actual site. Each specimen was divided into two parts. One part was fixed in a mixture of dehydrated alcohol and solution of formaldehyde for histologic preparations and for microincineration according to the technic of Scott,[42] while a second part was dissolved in triply distilled nitric acid for spectrographic analysis by the method of McMillen and Scott.[43] In some cases a third part was fixed in Zenker's solution (prepared with solution of formaldehyde) to obtain a better fixation of fats and proteins. Sections cut 6 microns thick were microincinerated, and comparative histologic preparations were stained by Masson's trichrome method[44] and with hematoxylin and eosin. All of these methods are described in detail elsewhere.[45]

Histology: The intercellular fibrils are decidedly altered in the entire epidermis of patients with pemphigus. Both in unaffected areas and in lesions of the same patient these fibrils differ conspicuously from those of normal skin taken from normal persons in that they adsorb both ponceau xylidine and acid fuchsin in Masson preparations much more intensely (fig. 4). Normal fibrils adsorb only the ponceau xylidine, while in pemphigus skin acid fuchsin is adsorbed intensely. The intercellular fibrils extending from the basal cell cytoplasm into the dermis are more heavily colored and longer than those of normal skin. Such a change in staining capacity probably indicates some fundamental physicochemical disorganization in the components of these fibrils. It is pertinent to note here that the length of the basal cell fibrils that extend into the dermis is as much as twice that of the fibrils between spinous cells. These abnormally long fibrils in pemphigus skin are evidently composed of some "foreign" material. Whatever the component substance of these basal fibrils, it is probably produced in far greater amounts at the dermal-epidermal junction than within the epidermis itself. It is, of course, questionable even in normal skin whether such basal cell–dermal fibrils would be passed by regeneration to spinous cells; hence, one may expect that the shorter fibrils of the spinous cells in pemphigus skin may have grown independently of

42. Scott, G. H.: The Localization of Mineral Salts in Cells of Some Mammalian Tissues by Microincineration, Am. J. Anat. **53**:243, 1933.

43. McMillen, J. H., and Scott, G. H.: An Interrupted Arc for Spectral Analyses, Rev. Scient. Instruments **8**:121, 1937.

44. Masson, P.: Carcinoids and Nerve Hyperplasia of the Appendicular Mucosa, Am. J. Path. **4**:181, 1928.

45. MacCardle, R. C.; Engman, M. F., Jr., and Engman, M. F.: (*a*) Spectrographic Analysis of Neurodermatitic Lesions: A Human Magnesium Deficiency, Arch. Dermat. & Syph. **44**:429 (Sept.) 1941; (*b*) Mineral Changes in Neurodermatitis Revealed by Microincineration, ibid. **47**:335, 1943. (*c*) footnote 41.

the longer basal cell fibrils. The nucleoli and most of the keratin in the corneal layer of pemphigus skin possess staining capacities similar to those of the intercellular fibrils. This would seem to support Ludford's contention [46] that there is a close relationship between keratinization, nucleoli and intercellular fibrils. Thus, when the intercellular fibrils are altered, as in pemphigus, so also are the keratin and nucleolar substances.

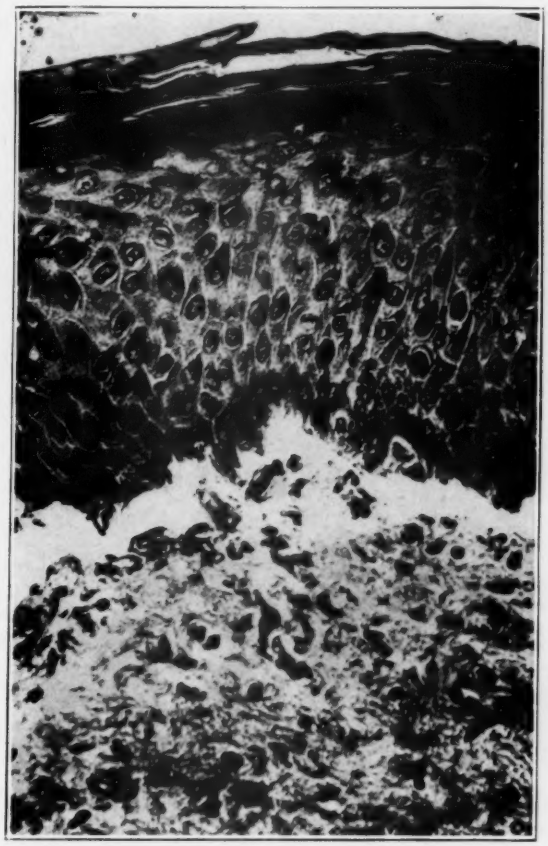

Fig. 4.—A bulla of pemphigus vulgaris, showing the edge of a vesicle with the intercellular fibrils intensely colored with acid fuchsin and some ponceau xylidine; note the subepidermal location of the bulla (Zenker's solution prepared with solution of formaldehyde; Masson's trichrome stain; × 900).

Either the collagenic substance of the outer third of the dermis is diminished greatly in amount or it fails to react in the usual way to aniline blue in Masson preparations. Both in unaffected areas and in lesions of the same patient the peripheral third of the dermis colors

46. Ludford, R. J.: Cell Organs During Keratinization in Normal and Malignant Growth, Quart. J. Micr. Sc. **69**:27, 1924.

only faintly or not at all with aniline blue, indicating a lack of collagenic substance of normal composition, while the deeper portion of the dermis is always heavily colored with aniline blue, indicating a heavy deposition of collagenic substance. The line of demarcation between the collagen-poor outer dermis and the collagen-rich deeper dermis is sharply distinct (fig. 5). The clear unstained outer dermis is usually compactly filled with a substance that is insoluble in solution of formaldehyde but evidently fairly soluble in alcohols and acetic acid. Even the substance coagulated in solution of formaldehyde fails to adsorb any of the dyes in Masson preparations. In a particular case of pemphigus, in which

Fig. 5.—Unaffected skin from a patient with pemphigus. Note the collagen-poor outer third of the dermis, which is faintly colored with aniline blue as compared with heavily colored deeper dermis (alcohol and solution of formaldehyde; Masson's trichrome stain; × 445).

sections of skin were fixed in solution of formaldehyde and potassium bichromate mixture and stained by the iron alum–hematoxylin method, this outer third of the epidermis consisted of thick strands of substance heavily colored with hematoxylin, whereas the collagen-rich deeper part of the dermis was stained only lightly with hematoxylin. All this seems to indicate that, although there are few if any large fat globules visible, the collagen-poor outer dermis of pemphigus is infiltrated with fine particles of lipoid "dust."

The formation of a vesicle in pemphigus evidently begins at the dermal-epidermal junction just underneath the basal cells. Small vesicles are always found to involve a separation of the epidermis from the dermis by the lifting off of the entire layer of basal cells (fig. 6), thus causing the intact epidermis to float on the surface of the progressively increasing volume of blister fluid under the basal layer and on the outer surface of the dermis. The dermal floor of the vesicle is stripped of epidermal cells, and in those instances in which basal cells are found on the floor of the vesicle regeneration probably accounts for their presence. Often small intraepidermal vesicles may be found in

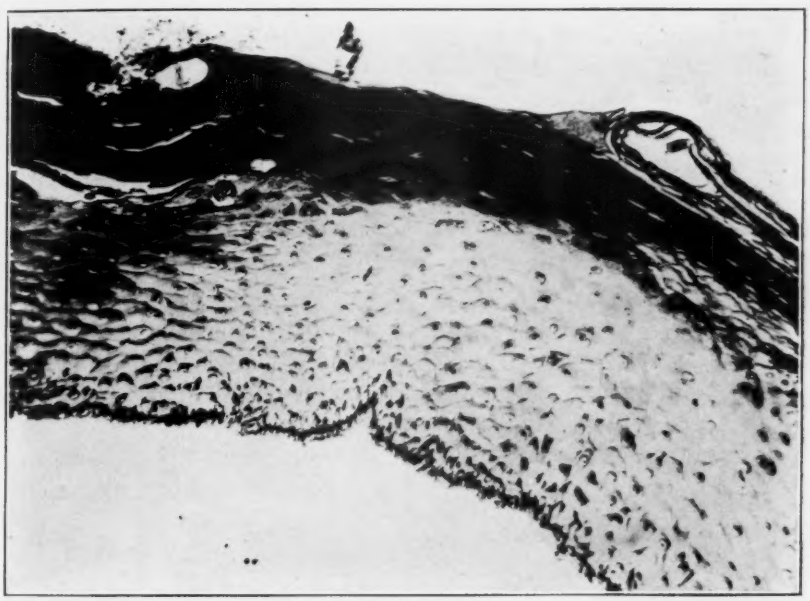

Fig. 6.—Separated epidermis floating above pemphigus vulgaris blister; note heavily stained basal cell fibrils (alcohol and solution of formaldehyde; Masson's trichrome stain; × 813).

the spinous layer of pemphigus skin, but if these are studied in serial sections they are found to be continuous vesicular spaces that lead into larger vesicles located under the epidermis. From a study of the serial sections, it is felt that all of these intraepidermal vesicles in pemphigus represent secondarily developed inroads into the spinous layer from the sides of vesicles originating on the surface of the dermis.

Localized clusters of small watery vacuoles may be frequently seen in the dermis immediately under the epidermis in the vicinity of a large vesicle or bulla. Such groups of water vacuoles are probably the forerunners of developing vesicles and bullae. In other areas the basal cell

cytoplasms overlying these dermal vacuoles are often swollen and full of intracytoplasmic vacuoles. The vacuolated basal cells are evidently in a more advanced stage of the formation of a vesicle and are most frequently seen in specimens of pemphigus skin taken from an area around the periphery of an already developed cluster of vesicles. Such vacuolated basal cells are few as compared with the large proportion of their neighboring cells which remain intact. They are probably the clear cells in the basal layer of normal epidermis.

There is little evidence of eosinophilia of the tissues in most of our specimens of pemphigus skin, although some show localized spots of infiltration with eosinophilic cells. There is much perivascular infiltration with round cells.

Microincineration: By incinerating a thin section of tissue at about 600 C., the carbon-containing compounds, such as proteins and fats, are burned off, leaving only the mineral skeletons of individual cells. Certain elements of biologic significance can be easily identified under dark field illumination. Calcium and magnesium leave a white ash. Silicon oxide appears of white gold color and is doubly refractive. Iron compounds are oxidized to a characteristically brilliant brick red ash. Sodium and potassium appear bluish gray. By this method the topographic distribution of minerals can be ascertained.

The outer third of the dermis in pemphigus is rich in silicon. The silicon of the dermis appears to have been mobilized from the deeper dermis to be deposited in huge quantities as silicocalcareous compounds in the outer third of the dermis (fig. 7). It may be seen in figure 7 that the line of demarcation between the ash-poor deeper dermis and the ash-rich outer dermis is as distinct as the demarcation in stained histologic preparations between the collagen-rich deeper dermis and the collagen-poor outer dermis. The ash-rich outer dermis in incinerated sections corresponds exactly to the collagen-poor outer dermis in stained sections. That a large part of the ash in the outer dermis is silicon is easily determined both by its color and by its double refractiveness under polarized light. The remainder is calcium and magnesium. *The mobilization of silicon and magnesium and calcium to the outer third of the dermis is a generalized phenomenon in pemphigus skin, not only in lesions but in unaffected areas.*

In areas of developing vacuoles and around vesicles and bullae silicon is especially abundant. Infiltrating blood cells and connective tissue cells contain largely the ash of calcium and magnesium.

The elongated intercellular fibrils are heavily mineralized largely with silicon (fig. 8). This is true in both affected and unaffected skin of patients with pemphigus. The nucleoli leave little white ash as compared with nucleoli of normal cells. In pemphigus skin the nucleoli

of the spinous cells contain no silicon. The keratin of the corneal layer leaves no white ash of calcium and magnesium. The only ash visible in the keratinized layer is the bluish gray ash of potassium and sodium and a few scattered particles of iron. In this respect the keratin of pemphigus is similar to that of baby skin.[45b]

In ashed skin of a normal person about 40 years of age the dermis contains evenly scattered strands of white ash of calcium and magnesium with considerable silicon.[45b] The intercellular fibrils leave little or no ash, and the nucleoli of the epidermis contain much silicon. The keratin layer is heavily laden with white ash of calcium, magnesium and silicon. In the skin of a normal person about 70 years of age there is almost no

Fig. 7.—Ashed unaffected skin from a patient with pemphigus (section adjacent to that in figure 4). Note deposition of white ash in the outer portion of the dermis with little in the deeper portion; most of the white ash is silicon, the remainder being calcium and magnesium (microincinerated; × 400).

silicon, but there is an abundance of calcium in the dermis. In baby skin the keratin layer leaves only a blue ash of potassium and sodium with little calcium and magnesium.

Incinerated pemphigus skin regardless of age shows that the dermis contains much excess silicon in its peripheral layer. Even skin from a 70 year old patient contains much silicon in the dermis. The keratin of pemphigus skin, like normal baby skin, leaves only residues of potassium and sodium after ashing. The nucleoli of the epidermis lack silicon.

Huge deposits of iron may be seen in the dermis around pemphigus blisters and in the intercellular fibrils in the epidermis. The nuclei of epidermal cells contain conspicuously large clumps of iron. There is also much iron found in the keratin layer. The intercellular fibrils, particularly the elongated ones extending from basal cells into the dermis, possess fine granules of iron residue along their entire lengths from their intracellular origins to their extracellular terminations in the dermal tissue. In unaffected skin the deposits of iron are confined largely to the intercellular fibrils and to connective tissue cells in the outer dermis.

Fig. 8.—Ashed separated epidermis floating above a pemphigus blister (section adjacent to that in figure 6). Note hypermineralization of basal cell fibrils with silicon. The corneum leaves little ash (microincinerated; × 850).

Most of the iron in pemphigus skin is organically active "masked" iron. This was determined by the use of Macallum's test [47] for "masked" iron. Sections of skin were also prepared by the prussian blue method,[48] by which only free inorganic iron is revealed. Such

47. Macallum, A. B.: On the Distribution of Assimilated Iron Compounds Other than Hemoglobin and Hematins in Animal and Vegetable Cells, Quart. J. Micr. Sc. **8**:175, 1895.

48. Gatenby, J. B.; Painter, T. S., and others: The Microtomist's Vade-Mecum (Bolles Lee), ed. 10, Philadelphia, P. Blakiston's Son & Co., 1937.

free inorganic iron is storage iron, which is probably available for fabrication of hemoglobin during regeneration of blood cells or respiratory compounds, whereas "masked" organically bound iron such as Macallum found in nucleoproteins is biologically active iron, taking part in cell metabolism. This "masked" iron is the kind found in Nissl bodies. Little inorganic iron can be revealed in the epidermis of pemphigus skin by the prussian blue test; some iron can be detected in the dermis of pemphigus skin by this method. In normal skin from normal persons nearly all of the iron except that of the nuclei is inorganic storage iron.[45b] In pemphigus skin (both lesions and unaffected areas) essentially all of the iron can be revealed histologically only by Macallum's test, showing that it is organically bound active iron. The iron in pemphigus skin is located primarily in the nuclei, in perinuclear cytoplasm and in the intercellular fibrils. The outer third of the dermis is also heavily mineralized with "masked" iron.

Spectrographic Analysis: Histospectrographic analyses were made on the whole skin of the patients studied. It was not until after this work was finished that Baumberger, Suntzeff and Cowdry [49] were able by application of heat to separate epidermis from dermis without disturbance of the chemical constituents.

1. Silicon: The total amount of silicon in the whole skin is decidedly increased over that of normal skin. This is especially so in patients with pemphigus 70 years of age. Silicon evidently not only is mobilized from one stratum of the dermis to another, as shown by microincineration, but is mobilized to the skin from the rest of the system, as revealed by this increase in silicon in the whole skin in the spectrogram. Measured microphotometrically, the amount of silicon in pemphigus skin is almost double the amount found in normal skin. In old pemphigus skin the order of magnitude of the increase is still greater than in younger adult skin.

2. Calcium: The content of calcium in pemphigus skin varies greatly from case to case. It is in no case decreased below the normal level. There is apparently no relationship between the variability of this element and the variability of any other element studied.

3. Magnesium: The quantity of magnesium in pemphigus skin is quite within the normal range in every case of pemphigus.

4. Manganese: In all but 1 of our cases the manganese lines of radiation on the spectrograms were intensely black, indicating a relatively consistent deposit of manganese in pemphigus skin. In normal skin manganese is more often absent than present. This element is evidently

49. Baumberger, J. P.; Suntzeff, V., and Cowdry, E. V.: Methods for the Separation of Epidermis from Dermis and Some Physiologic and Chemical Properties of Isolated Epidermis, J. Nat. Cancer Inst. **2**:413, 1942.

not maintained at a constant level in normal skin. But in both unaffected areas and lesions of pemphigus skin, the manganese content is maintained at a high level.

5. Iron: The iron content of the skin in every one of our cases of pemphigus was higher than in normal skin. Regardless of the amount of blood present in the tissue the total iron content of the whole skin does not vary significantly from its usually high value. There is about twice as much iron present in pemphigus skin as in normal skin. As revealed by microincineration, a large proportion of this iron is located in the intercellular fibrils and in the cellular components of the connective tissue in the dermis. A good deal of it is also found discarded in the keratin. The most striking characteristic of this excessive increase of iron in pemphigus skin is that unaffected areas of pemphigus skin as well as early developing vacuolated areas contain as much iron as do active lesions. The iron in pemphigus skin must be combined organically in a biologically active state so that it is being constantly utilized and not allowed to accumulate in permanently deposited masses of useless metabolites.

6. Copper: Copper is found in all pemphigus skin. Its quantity is essentially within the normal range. Normal skin, however, frequently lacks this element.

7. Cobalt: This element was present in most of our cases of pemphigus lesions, but none is found in unaffected skin. It is rarely present in normal skin in sufficiently large quantity to be detected accurately by spectrographic analysis.

8. Phosphorus: Phosphorus is found in large quantities in all cases of pemphigus. Its amount is not to be considered unusual, however.

9. Selenium: Selenium has been found in all cases of pemphigus. It has not been found in any of the specimens of normal skin.

10. Zinc: This element varies in pemphigus. In some cases it is barely detectable, while in others the zinc lines are striking. Zinc is always present in pemphigus skin, although its variations are not unusual.

Nikolsky's Sign.—"Nikolsky's sign" was induced in 2 cases of pemphigus vulgaris, and specimens of the damaged skin were immediately removed for study of the location of the separation and for observations of histochemical changes. It was found that the epidermis was separated from the dermis at the epidermal-dermal junction, leaving the dermis completely stripped of its basal cells. The still attached elongated intercellular fibrils of the basal cells were left dangling free and intact in the intervening artificial space between the separated basal cells and the free edge of the dermis. In 1 of these 2 cases of pemphigus

the epidermal-dermal break extended from its sides up into the spinous layer of cells, so that it would have been possible to pass a small probe from the injury space (between the stripped dermis and the overhanging basal cells) into a continuous space extending upward between the layers of the spinous cells (within the epidermis).

The mineral picture revealed by microincineration and spectrographic analysis is no different from that found in unaffected skin removed without previous induction of Nikolsky's sign.

It should be pointed out that the whole epidermis and the artificially formed space beneath it are permeated with a collagen-like substance that adsorbs aniline blue readily.

Cantharides Blisters.—An attempt was made to compare artificially induced blisters with pathologically formed pemphigus blisters. Cantharides blisters were induced by the application of 2 mm. patches of cantharides plaster to the unaffected skin of patients without pemphigus. Specimens for biopsy were taken immediately after contacts varying from six to thirteen hours.

In such instances a vesicle is formed by vacuolation of the cytoplasm of the spinous cells and by intracellular edema. The vesicle is then formed by a separation of spinous cells from one another, due probably to the pressure of excessive accumulation of water and to dissolution of certain cellular components. The intercellular fibrils in these areas of preliminary vacuolation remain visible but fail to absorb any of the dyes used in Masson preparations. The exudate forming the vesicular fluid is probably mainly water, leaving little material that is stainable. The general histologic picture of the surrounding areas is that of normal skin, excepting of course the inflammatory reaction.

The mineral changes in cantharides blisters are not significant. There is an increase in calcium and iron, as determined spectrographically, which can be seen in microincinerated sections to be due largely to invading blood and connective tissue cells which are loaded with calcium and iron residues.

COMMENT

The Genesis of a Pemphigus Bulla.—From the foregoing study of pemphigus vulgaris, it is clear that cutaneous vesicles in this disease originate as small vacuoles in the dermis immediately beneath the basal cells of the epidermis and, further, that the primary focus of weakening is evidently to be found at the epidermal-dermal junction, where the basal cell cytoplasmic fibrils interweave the strands of dermal substance. The accumulating blister fluid pushes the intact epidermis off its dermal moorings so that the dermal edges of the basal cells and their attached filamentous fibrils dangle freely on the surface of the blister fluid, leaving the outer limits of the dermis stripped free of germinative

epidermal cells. Thus the bulla is formed beneath the epidermis, and only secondarily do sidewise rifts occur between spinous cells, which spaces if not studied in serial sections give the deceiving appearance of being the intraepidermal birthplaces of bullae.

The development of a single bulla in pemphigus vulgaris evidently occurs as follows: In the first place, the preliminary site of vesicle formation in the periphery of the dermis in unaffected pemphigus skin is altered in such a way that its collagenic substance is replaced by a lipoprotein which not only possesses little adhesive property but is highly autoxidizable and in the absence of the proper proportion of free cholesterol is dangerously hydrophilic. This lipoprotein in excessively abnormal quantities in the outer third of the dermis is infiltrated with large quantities of silicon and iron, as well as with "trace elements," such as manganese, selenium, cobalt and zinc in quantities of questionable toxicity. In addition to this alteration in the dermis, the filamentous fibrils of the basal cells are elongated and contain lipoprotein that is infiltrated with excess quantities of iron and silicon. The etiologic factors inducing such cytologic changes as the replacement of comparatively hydrophobic collagen with a highly hydrophilic lipoprotein matrix are of course unknown. Dietary factors should be investigated more thoroughly in regard to pemphigus.

In this lipoprotein dermal matrix which apparently becomes increasingly hydrophilic, small watery vacuoles form among the meshes of the filamentous fibrils protruding from the basal cells into the dermis. These vacuoles subsequently increase in size and coalesce to form a larger subepidermal vesicle. Evidently adjacent vesicles coalesce to form a single large subepidermal bulla. A bulla then evidently originates from several localized groups of small vacuoles. The sidewise pressure of a bulla then later causes rifts within and under the weakened epidermis, and these rifts afford channels of communication with other bullae to form large intraepidermal and subepidermal blisters.

The center of the primary reactions in the formation of a bulla in pemphigus skin is evidently located in the outer third of the dermis at the epidermal-dermal junction. It is at this point that the smallest vacuoles form, and it is here also that so many histochemical changes occur prior to the development of a vesicle. Studies of an induced Nikolsky phenomenon with slipping of the epidermis show that the weakest spot is at the epidermal-dermal junction, where separation of epidermis from dermis occurs. Artificially induced cantharides blisters in normal skin originate intraepidermally, the stimulus being externally applied. The question as to whether or not cantharides blisters would arise intraepidermally in patients with pemphigus has not been tested. There are many problems about the development of this weakened epidermal-dermal focus in pemphigus. Why, for instance, is the skin

capable of producing normal collagenic substance in the deep portion of the dermis and not in the peripheral portion? The role of infiltrating minerals, such as silicon and manganese, in excess quantities is wholly unknown. Do the rate of intake of certain dietary elements and the rate of metabolism of the same influence the onset of an attack?

The appearance of bullae as a manifestation of a local disturbance is of relatively infrequent occurrence, if one considers the potentialities the skin has for such phenomena. Thus, it may be logical to consider it more strange that bullae form so seldom than that they form so often. The area of the epidermis is from 60 to 90 per cent greater than that of the dermis [49]; there is a capillary hydrostatic pressure which can be liberated by an increased permeability to force fluid into the dermal spaces, separate the epidermis and form a bulla. What are the forces which ordinarily prevent the formation of bullae? These may be: (1) the normal relative impermeability of the capillaries to serum protein and the consequent reduction of effective capillary hydrostatic pressure to a minimum, (2) the resorption of filtered fluid from the arterial capillaries by the venous and lymph capillaries, (3) the strength of adhesion of the epidermis to the dermis, (4) the fluid capacity of the dermis, (5) the amount of fluid in interstitial spaces and (6) the state of water (bound or unbound) in interstitial spaces.

What conditions in pemphigus are conducive to bullous formation?

1. The epidermis is held to the dermis less firmly. This condition is seen in the ease with which the epidermis can be rubbed off in eliciting the Nikolsky sign. Further, the histologic preparations previously described show a deficiency in normal-staining collagen. Also, one must now consider the work of Baumberger, Suntzeff and Cowdry,[49] who in attempting to improve the acetic acid method of epidermal separation found some interesting and pertinent effects of chemicals and heat on the epidermis and epidermal-dermal junction. They worked on the hypothesis that collagen or "hide powder" behaves like gelatin and swells on alteration of p_H to either side of the isoelectric point, thus facilitating the separation of the epidermis from the dermis. They tried to induce separation by various simple compounds. One of the most practical and efficient agents was found to be an iso-osmotic (or approximately one-third normal) solution of ammonium hydroxide. When this is applied to recently excised human skin for thirty-five minutes the epidermis can be removed at the dermal-epidermal junction; shorter contact allows separation between the basal and malpighian layers. They also found that by placing the skin, cutis down, on a hot plate carefully regulated at 49.2 C. (126 F.) after two minutes the entire epidermis could be removed easily by blunt dissection. It is significant that if either recently excised or intact living skin is treated

with the ammonium hydroxide solution sufficiently long so that separation between the dermis and the basal cell layer can be accomplished and if the skin so treated is thoroughly rinsed with Ringer-Locke solution there occurs a reattachment of the basal cell layer to the corium, although the rete layer can still be separated from the basal cell layer. Similarly, the heat-treated (necessarily excised) skin when allowed to cool becomes reattached at the dermal-epidermal junction, and under blunt dissection the epidermis can be removed down to but not including the basal layer. From this we may assume that two things are true: (*a*) *the method by which the upper layers of the epidermis are attached to themselves or to the basal layer involves an irreversible reaction,* and (*b*) *the method of attachment at the dermal-epidermal junction is attended with a reversible reaction,* a factor in favor of a substance such as gelatin (collagen) being the active agent.

2. The dermis in pemphigus contains more fluid than normal dermis. This is apparent from the fact that the extracellular fluid in pemphigus averages 20 per cent above normal. As a result of this distention with fluid, the movement of filtrate from the blood capillaries can occur more freely through capillary spaces [23] between elastic and collagenic fibers to accumulate in minute vesicles, coalesce and form bullae.

3. The gel binding the interstitial fluid may be broken down. It is generally believed (Bensley [50]) that a "hyaline" substance occurs in the interstices of dermis and subcutaneous tissue holding all the water present in a gel. Recently McClean,[51] Chain and Duthie,[52] and Meyer and Chaffee [53] have discovered an enzyme in skin called hyaluronidase, which diminishes the viscosity of the mucopolysaccharides extractable from skin and which also increases the spread of intradermally injected hemoglobin. It may be that bullae are formed where locally this enzyme (hyaluronidase) depolymerizes and hydrolyzes a mucopolysaccharide gel of the dermis, leaving the water of the gel free as a blister fluid right at the site of the bulla. Such a hypothesis would account for the rapid appearance of blister fluid from a tissue through which water cannot be forced hydrostatically at any appreciable speed. It would also agree with the fact that vascular changes may be absent at the site of bulla formation. Unfortunately, we have not had enough experience with this procedure to draw any conclusions. However, the results are promising, as will be shown.

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50. Bensley, S. H.: On the Presence, Properties and Distribution of the Intercellular Ground Substance of Loose Connective Tissue, Anat. Rec. **60**:93, 1934.

51. McClean, D.: Studies on Diffusing Factor, Biochem. J. **35**:159, 1941.

52. Chain, E., and Duthie, E. S.: Identity of Hyaluronidase and Spreading Factor, Brit. J. Exper. Path. **21**:324, 1940.

53. Meyer, K., and Chaffee, E.: The Mucopolysaccharides of Skin, J. Biol. Chem. **138**:491, 1941.

Sterile citrated blood from the patient to be tested is centrifuged and the plasma removed. After several washings with physiologic solution of sodium chloride the cells are hemolyzed with distilled water and the stroma removed by centrifuging and decanting. Then 0.3 to 0.5 cc. of this solution is injected intradermally, and the spreading of the color is observed at intervals to twenty-four hours. Use of ultraviolet radiation aids in reading the size of the reaction.

The intradermal injection of 0.3 cc. of the patient's own hemoglobin in two places on the lateral aspect of the thigh of a patient with pemphigus caused spots about 10 mm. in diameter in six hours, increasing to 45 and 40 mm. in diameter in twenty hours. In a normal patient the injection of her own hemoglobin in a similar location elicited reactions with diameters of 9 and 10 mm. after an hour, increasing to 18 and 15 mm. in twenty hours. It is obvious that the area of spread in the patient with pemphigus was much greater than in the normal person.

The Probable Role of Silicon.—Silicon is universally present in plant and animal tissues.[54] That it is a biologically essential element in living protoplasm is questionable. Silicon is not very active chemically. Organically it is undoubtedly combined as silicocalcareous proteinates. This element is always present in tuberculous lesions. Its crystals are capable of injuring cells, and it is believed by some investigators that in excess quantities silicon provides the necrotic sites for multiplication of the tubercle bacillus. Silicosis is often concomitant with pulmonary tuberculosis. Silicon is evidently related to healing processes, for it is always found in huge quantities in scar tissue, and fibrosarcomas contain large amounts of silicon. During the development of a cutaneous lesion of neurodermatitis the nucleoli of epidermal cells lack silicon, but they regain this element during healing. In severe nephritis there are a preliminary lipoprotein degeneration and cloudy swelling followed by rapid fibrotic growth with deposition of silicon. References for these statements may be found in the excellent review by King and Belt [54] on the physiologic and pathologic aspects of silica.

In pemphigus vulgaris, not only is silicon mobilized in huge quantities from the deep dermis to the center of primary lesion in the outer dermis, but also this element is transported by the blood stream to the skin in larger quantities than normally occurs. The dermis of pemphigus skin is full of new fibrous tissue as a result of the constant destruction of skin by vesiculation and rebuilding of it in healing processes. Perhaps silicon is mobilized to promote fibrosis in a skin that is constantly being altered even in unaffected areas. Furthermore, the damage done by

54. King, E. J., and Belt, T. H.: The Physiological and Pathological Aspects of Silica, Physiol. Rev. **18**:329, 1938.

silicon crystals may well induce the mobilization of the lipoprotein substance in the outer dermis and thus be the cause of one of the most conspicuous histochemical changes. However, such deductions are almost purely speculative and must be investigated further. At present there is no experimental evidence to show whether silicon is biologically active or whether its presence is merely adventitious.

The Nature of Iron in Pemphigus Skin.—The epidermis and the lipoid outer dermis in the skin of a patient with pemphigus contain unusually large amounts of "masked" organically bound iron. Much of this organic iron is found in the nuclei and perinuclear cytoplasm of the epidermal cells, and intercellular fibrils of the basal cells are heavily laden with organically compounded iron. The iron in the lipoprotein matrix of the dermis is fairly homogeneously distributed and probably bound with phospholipid-protein compounds. Deposits of inorganic free iron, demonstrable by the ordinary prussian blue reaction and generally called storage iron, vary greatly in amount and distribution both in the epidermis and in the dermis, whereas the distribution and amount of "masked" organic iron are comparatively constant in all pemphigus skin.

Nearly all of the iron in normal skin is inorganic storage iron and is readily detectable by the prussian blue reaction. Normal skin of normal persons contains a small relatively constant amount of "masked" organic active iron, deposited in the nuclei of the epidermis, and a certain highly variable amount of inorganic storage iron, found largely in macrophagic cells of the dermis and sometimes in the keratinized layer of the epidermis. The iron of the keratin is probably of extraneous origin, however, rather than an excretory product of endogenous metabolism. The cytoplasms of epidermal cells in normal skin contain little iron of any kind, as compared with the large amounts of cytoplasmic iron found in pemphigus epidermis. Normal intercellular fibrils contain no iron, while in pemphigus skin these fibrils are heavily laden with organically bound iron. The matrix of the dermis in normal skin contains little if any detectable "masked" organic iron.

The transformations which iron undergoes during its metabolism in the animal body have not yet been completely revealed. Little can be said concerning the nature of intracellular iron. Whether part or all of it is of a cytochrome nature has yet to be divulged. Keilin,[55] who studied MacMunn's histohematin and renamed it cytochrome, has shown that it contains iron in the form of a hemochromogen and is present in all animal cells. Anson and Mirsky [56] have shown that Warburg's

55. Keilin, D.: Cytochrome and Intracellular Oxidase, Proc. Roy. Soc., London, s.B **106**:418, 1929.

56. Anson, M. L., and Mirsky, A. E.: Heme and Tissue Iron, J. Gen. Physiol. **12**:401, 1929.

respiratory enzyme is not only a heavy metal compound but in particular a heme compound. Macallum found that the chromatin of the nucleus contains iron which is so firmly bound to nucleoproteins that it must first be liberated by extraction with an acid in order to be detected histochemically by the prussian blue reaction. Such "masked" iron is also found in the protein-phospholipid constituents of the Nissl substance, which is highly sensitive to physiologic changes in the nerve cell. De Robertis [57] even found iron within large mitochondria, which are reputedly composed for the most part of phospholipids, cholesterol and proteins.

The origin and fate of the large amount of organically bound iron in pemphigus skin remains a mystery, although its functional importance can hardly be questioned in view of the tenacity with which such pathologic tissue holds it. That this iron is not utilized for the fabrication of blood hemoglobin is evidenced by the fact that little or no change occurs in the hemoglobin content in a patient with pemphigus. The excess iron in pemphigus skin is for the most part already in the form of an active organically bound intracellular compound similar to cytochrome or Macallum's nucleoprotein iron compound. It is probably active in some oxidative mechanism. Whether or not pemphigus skin has a high oxidative rate is unknown, but the presence of excess organic iron with copper and manganese would be conducive to an increase in metabolism. It is pertinent to note that 4 of our patients received many intravenous injections of iron cacodylate, while the other 4 received no iron therapy. The presence of large quantities of organically bound iron in pemphigus skin may be of significance in regard to the metabolic history of iron and arsenic introduced in such compounds.

Nikolsky's Sign.—Throughout this paper we have used the term Nikolsky sign in the loose sense, according to common usage. If one attempts to find an adequate definition or explanation of this phenomenon, one soon learns that even though the term is frequently applied there is little written on the subject. Therefore, in connection with our histologic studies, it is necessary to consider the thesis of Nikolsky,[58] which appeared in 1896 under the title of "Pemphigus Foliaceus." [59]

In the course of this lengthy manuscript Nikolsky described his famous sign, the weakening of connection between the corneal and rete layers of involved and normal-appearing skin in cases of pemphigus foliaceus. He strongly emphasized a distinction of pemphigus foliaceus

57. de Robertis, E.: Estudios de histofisiologia hepatica, Buenos Aires, G. Buffarini, 1939.

58. Nikolsky, P. V.: Materïali k ucheniyu o pemphigus foliaceus Cazenavi [Pemphigus Foliaceus], Thesis, Kïev, V. I. Zavadzki, 1896.

59. Dr. V. Suntzeff, of the Barnard Free Skin and Cancer Hospital, translated Nikolsky's thesis.

from pemphigus vulgaris, and in the differential diagnosis of the two diseases he proposed his three criteria for the well known Nikolsky sign: First, in pemphigus foliaceus the stratum corneum when pulled can be stripped off over large areas, whereas in pemphigus vulgaris it is possible to strip only a limited area, which is really the exact area of the blister, the neighboring skin being absolutely normal. Secondly, in pemphigus foliaceus if the normal-appearing areas between the lesions on the skin are rubbed the corneum comes off, while in pemphigus vulgaris if the lesions are healed the epidermis cannot be rubbed off. Thirdly, if in a case in which a diagnosis has not been made it is possible by rubbing to remove the corneum of healthy uninvolved skin, then the patient may be said to have pemphigus foliaceus. In pemphigus vulgaris the skin covered with firm keratin can be separated only where there are bullae.

Nikolsky went so far as to state that this weakening of the connection between the corneal and malpighian layers in pemphigus foliaceus is an absolute differential characteristic which distinguishes pemphigus foliaceus from any other disease; furthermore, the diagnosis of pemphigus foliaceus should not be made in the absence of the sign. He said that pemphigus vulgaris not only lacks the sign but forms the blister usually at the dermal-epidermal junction.

Thus, Nikolsky defined his sign specifically and emphatically intended it to be used as a differential diagnostic feature of pemphigus foliaceus. Common usage has applied the procedure to and made it a diagnostic feature of pemphigus vulgaris, in direct contradiction to Nikolsky's intentions. By strict application of his criterion, Nikolsky considered pemphigus vulgaris to have a negative sign. However, the procedure for the sign (rubbing the skin) remains the same and is of some clinical importance in pemphigus vulgaris. The methodical procedure of attempting to rub off the epidermis should be considered as the Nikolsky test, whereas the term Nikolsky sign should be used to designate a positive result of separation between the corneal and malpighian layers after application of the test. We have shown that the Nikolsky test applied to a patient with pemphigus vulgaris gives a separation at the dermal-epidermal junction. Although we have not made a particular study of this, we have observed that some other diseases, notably erythema multiforme bullosum, respond to Nikolsky's test in the same way as pemphigus vulgaris.

SUMMARY

1. Attempts to form bullae show that hydrostatic pressure acting on altered corium is not the primary factor in the formation of a pemphigus bulla.

2. Cohesion in pemphigus skin is found to be good despite the presence of "Nikolsky's sign."

3. Polarographic studies fail to reveal any changes in bullous fluid as compared with normal serums. No differences between the ratios of cysteine-cystine to nitrogen of normal and of pemphigus epidermis could be detected.

4. The minerals and other constituents of 28 biopsy specimens of both lesions and unaffected skin of 8 patients with pemphigus vulgaris were studied histochemically by ordinary histologic technics and by microincineration and spectrographic analysis. Comparisons were made with 83 specimens of normal skin and 55 specimens of pathologic skin from 13 patients with other diseases of the skin.

5. The collagenic substance in the outer third of the dermis in both unaffected skin and lesions of pemphigus is replaced by a lipoprotein.

6. The intercellular fibrils of basal cells of pemphigus skin are elongated and altered physicochemically and contain lipoprotein infiltrated with large amounts of silicon and other elements.

7. Both lesions and unaffected skin in pemphigus contain increased amounts of iron in the epidermis and in the matrix of the dermis. Most of the iron is in the form of "masked" organic iron, with but little inorganic storage iron.

8. Silicon is mobilized from the deeper part of the dermis to the outer third, and probably from the whole body to the skin. It is suggested that the role of silicon is concerned in healing and fibrosis, although its crystals may be responsible for the formation of the lipoprotein "foam" in the outer portion of the dermis.

9. Bullae in pemphigus vulgaris are formed subepidermally in the peripheral third of the dermis. A vesicle forms by coalescence of several vacuoles originating in the dermis among the meshes of the fibrils of basal cells.

10. The entire skin of a patient with pemphigus contains increased amounts of silicon, iron, manganese and selenium.

11. It is suggested that the term Nikolsky's sign be restricted to the phenomenon of separation of the corneum from the rete in pemphigus foliaceus. The term Nikolsky's test should be used to designate the procedure of testing the degree of resistance of the epidermis to slipping.

12. In pemphigus vulgaris, as well as in certain other diseases of the skin, the reaction to "Nikolsky's test," if effected, is a slipping at the dermal-epidermal junction.

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TINEA VERSICOLOR INVOLVING THE SCALP

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The favorite location of pityriasis versicolor is the upper part of the trunk. However, the disease may begin in or spread to other parts of the skin. Thus, its location in the follicular orifices has been recorded by McEwen,[1] Aleixo[2] and Perin and Langlois[3]; in the plantar region, by Smith[4]; in the palmar region, by Gottheil[5]; on the nails, by Campana[6]; on the dorsa of the hands and forearms, by Orsini[7]; in the inguinal and inguinocrural regions, by Perin and Langlois[8] and Moore[8]; on the internal surfaces of the thighs, by Aleixo[9]; on the female breast, by Rietman[10]; on the face, by Biart,[11] Smith,[12] Gottheil,[13]

1. McEwen, E. L.: Tinea Versicolor: Unusual Case with Lichenoid Folliculitis, J. Cutan. Dis. **29**:19, 1911.

2. Aleixo, A.: Dermatomycoses em Bello Horizonte, Primeiro Congresso sul-Americano de dermatologia e sifilografia, Rio de Janeiro, Imprensa Nacional, 1921, p. 294.

3. Perin, L., and Langlois, L.: Pityriasis versicolor à forme folliculaire, Bull. Soc. franç. de dermat. et syph. **40**:1318 and 1371, 1933.

4. Smith, E. D.: A Rare Case of Tinea Versicolor, New York M. J. **64**: 583, 1896.

5. Gottheil: A Unique Case of Pityriasis Versicolor, M. Rec., New York **56**:15, 1899.

6. Campana, cited by Dubreuilh.[19]

7. Orsini, O.: Personal communication to the author.

8. Moore, M.: Pityriasis Versicolor Involving the Inguinal Region and the Genito-Crural Folds, Arch. Dermat. & Syph. **38**:249 (Aug.) 1938.

9. Aleixo, A.: Personal communication to the author.

10. Rietman, B.: Pityriasis versicolor à forme anormale, Bull. Soc. franç. de dermat. et syph. **31**:20, 1924.

11. Biart, cited by Sutton, R. L., and Sutton, R. L., Jr.: Diseases of the Skin, ed. 10, St. Louis, C. V. Mosby Company, 1939, p. 1102.

12. Smith, cited by Sutton, R. L., and Sutton, R. L., Jr.: Diseases of the Skin, ed. 10, St. Louis, C. V. Mosby Company, 1939, p. 1102.

13. Gottheil, cited by Sutton, R. L., and Sutton, R. L., Jr.: Diseases of the Skin, ed. 10, St. Louis, C. V. Mosby Company, 1939, p. 1102.

Allen,[14] Sidlick and Corson,[15] Besnier,[16] Payne,[17] Arton,[18] Dubreuilh [19] and Aleixo [2]; in the folds of the joints, by Gougerot, Blum and Duché,[20] and in the cervical region, by Unna [21] and Allen.[22]

With regard to the scalp we have found, after a careful examination of the medical literature of the world available to us, the following recorded cases: 20 cases by Shoji [23] in 1926; 1 case by Keller [24] in 1926; 14 cases by Suzuki [25] and Matsumoto [26] in 1928; 1 case by Payne [27] in 1929; 3 cases by Kaschkin [28] in 1929; 1 case by Ballo [29] in 1930; 2 cases by Pisacane [30] in 1937 and 1 case by Baer [31] in 1938—a total of 43 cases.

It is found that the location of the disease (especially on the cheek and scalp) varies in different countries. Facial location of pityriasis versicolor is frequent in Brazil (fig. 1) though rare in other countries.

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14. Allen, cited by Sutton, R. L., and Sutton, R. L., Jr.: Diseases of the Skin, ed. 10, St. Louis, C. V. Mosby Company, 1939, p. 1102.

15. Sidlick, D. M., and Corson, E. F.: Tinea Versicolor of Face, Arch. Dermat. & Syph. **5**:604 (May) 1922.

16. Besnier, cited by Ruett, A., in Jadassohn, J.: Handbuch der Haut- und Geschlechtskrankheiten, Berlin, Julius Springer, 1928, vol. 11, p. 696.

17. Payne, cited by Dubreuilh.[19]

18. Arton, M.: Contributo allo studio della pityriasis versicolor acromizzante, Gior. ital. di dermat. e sif. **71**:1945, 1930.

19. Dubreuilh, W.: Precis de dermatologie, ed. 4, Paris, Octave Doin et fils, 1917, p. 85.

20. Gougerot, H.; Blum, P., and Duché, J.: Polyépidermo-mycose des plis et disséminée avec intégrité du fond des plis: Epidermophyton inguinale, Malassezia furfur, Aspergilopsis, Bull. Soc. franç. de dermat. et syph. **39**:157, 1932.

21. Unna, cited by Dubreuilh.[19]

22. Allen, cited by Dubreuilh.[19]

23. Shoji, G.: Ueber die Pityriasis auf der behaarten Kopfhaut, Acta dermat. **7**:463, 1926.

24. Keller, P.: Fluorescenzenserscheinung und der menschlichen Haut, Dermat. Wchnschr. **82**:457, 1926.

25. Suzuki, Y.: Unusual Locations of Pityriasis Versicolor, J. Orient. Med. **8**:97, 1928.

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27. Payne, cited by Hudelo, L., and Rivalier, E.: Dermatologie: Pityriasis versicolor, in Laffont, A., and Durieux, F.: Encyclopédie médico-chirurgicale, Paris, Encyclopédie Medico-Chirurgicale, 1936, vol. 12, pt. 1, p. 12022.

28. Kaschkin, P. N.: Pityriasis versicolor des behaarten Kopfes, Dermat. Wchnschr. **88**:837, 1929.

29. Ballo, A.: Livre d'or de Beck Emlekkönyv, 1930, p. 533; cited by Gougerot, H.: Pityriasis Versicolor, in Darier, J., and others: Nouvelle pratique dermatologique, Paris, Masson & Cie, 1936, vol. 2, pt. 2, p. 223.

30. Pisacane, C.: Contributo allo studio delle epidermomicosi acromizzanti, Gior. ital. di dermat. e sif **78**:1155, 1937.

31. Baer, R. L.: Tinea Versicolor Involving the Scalp, Arch. Dermat. & Syph. **37**:970 (June) 1938.

Aleixo,[32] commenting on one of our observations, said that the lack of hygiene among certain persons explains the wide extent of pityriasis versicolor in Brazil. It is no wonder that the disease frequently involves the cheeks in persons who are careless about bodily cleanliness and even about washing their faces. After involving the cheek the disease may spread to the scalp, where it finds favorable conditions of humidity and

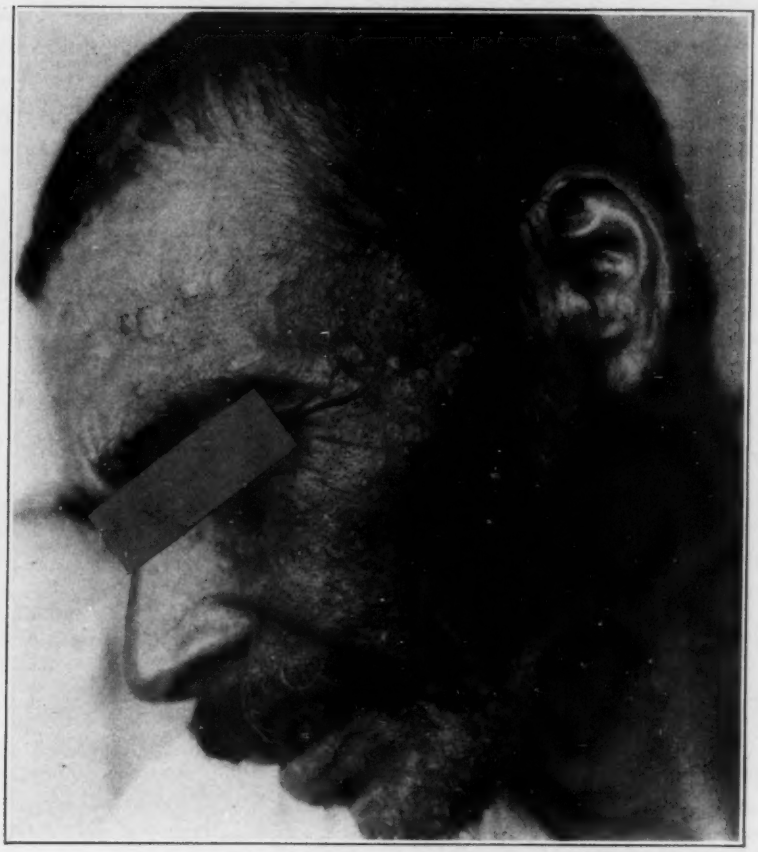

Fig. 1.—Tinea versicolor: frontofacial location.

may be mistaken for other forms of pityriasis. In 2 of our cases the disease spread to the scalp from the neck and in 1 case from the cheek. In all of our cases the disease has been a secondary one. Carelessness as regards treatment also favors the spread of the dermatosis.

Two of our patients were Negroes, and their unhygienic habits, we think, have helped to bring about the occurrence of the dermatosis on

32. Aleixo, A., in discussion on Costa, O. G.: Pityriasis Versicolor Involving the Scalp, Soc. med.-cirurg. Hosp. mil., Minas Geraes **53**:12, 1935.

the scalp. Besnier and Doyon in a marginal note in Kaposi's book [33] affirmed that cleanliness of the skin is sufficient to prevent the extension of the parasitic growth. However, we cannot say whether the patients observed in other countries were also careless in their personal hygiene.

Baer, in view of the frequency of pityriasis versicolor in Japan and China, suggested that the difference of secretions and difference of hair type between the Caucasian and Mongolian races may explain the large number of cases of involvement of the scalp recorded in those countries by Shoji and Matsumoto, who were indeed the first to call attention to this location.

In the United States only 1 case, reported by Baer, has been recorded. Our 3 cases are the first recorded in Brazil, and we believe that no other reference to the disease exists in the other South American countries. In our cases Besnier's sign, also known as the finger nail or Hobel's phenomenon,[34] was present on the diseased scalp as well as the glabrous skin.

No cultures were made of material taken from the scalps of our patients, for in spite of the attempts made by Magalhães and Neves [35] it has thus far been impossible to obtain cultures of Malassezia furfur in Brazil, in contrast to the positive results obtained abroad by Gastou and Nicolau,[36] Matzenauer [37] and Moore.[38]

In our cases the reactions to trichophytin and oidiomycin tests were negative. A biopsy was made only in case 3, but the direct microscopic examination of material in lactophenol showed numerous forms of M. furfur in all our patients, both in the lesions on the glabrous parts and in those on the scalp.

REPORT OF CASES

CASE 1.—D. G., a 10 year old Negro boy, a Brazilian, resided in Bello Horizonte. The family and personal histories were noncontributory. He had had for the last six months a scaly eruption on the scalp (fig. 2) and neck, in the interscapular space and along the border of the scalp and glabrous skin. The glabrous skin showed round, café au lait spots with furfuraceous scaling, no

33. Kaposi, M.: Lęcons sur les maladies de la peau, translated by E. Besnier and A. Doyon, Paris, G. Masson, 1881, vol. 2, p. 451.

34. Fontana, A.: Dermatologia, Turin, Unione tipografico, editrice torinese, 1936, p. 523.

35. Magalhães, O., and Neves, A.: Ensaios de mycologia: Contribuição para o estudo dos cogumelos em Belo Horizonte, Mem. Inst. Oswaldo Cruz **19**:245, 1926.

36. Gastou, P., and Nicolau: Culture du Microsporon furfur sur milieu solide placentaire, Bull. Soc. franç. de dermat. et syph. **13**:222, 1902.

37. Matzenauer, R.: Zur Bacteriologie der Pityriasis versicolor, Arch. f. Dermat. u. Syph. **56**:163, 1901.

38. Moore, M.: Cultivation of Malassezia Furfur, Etiological Agent of Pityriasis (Tinea) Versicolor, Mycopathologia **1**:53, 1938; Malassezia Furfur, the Cause of Tinea Versicolor: Cultivation of Organism and Experimental Production of Disease, Arch. Dermat. & Syph. **41**:253 (Feb.) 1940.

itching and a positive finger nail phenomenon. On the scalp the disease presented itself in a diffuse form with scaling, positive finger nail phenomenon and slight itching. The eruption was more evident in the occipital and parietal regions and at the boundary line between the scalp and glabrous parts, forming a true pityriasic border.

The reactions to trichophytin (1 : 30 solution) and oidiomycin (1 : 100 solution) tests were negative.

Mycologic examination was made by Dr. Neves, who found several examples of M. furfur in scales obtained from the scalp and interscapular region.

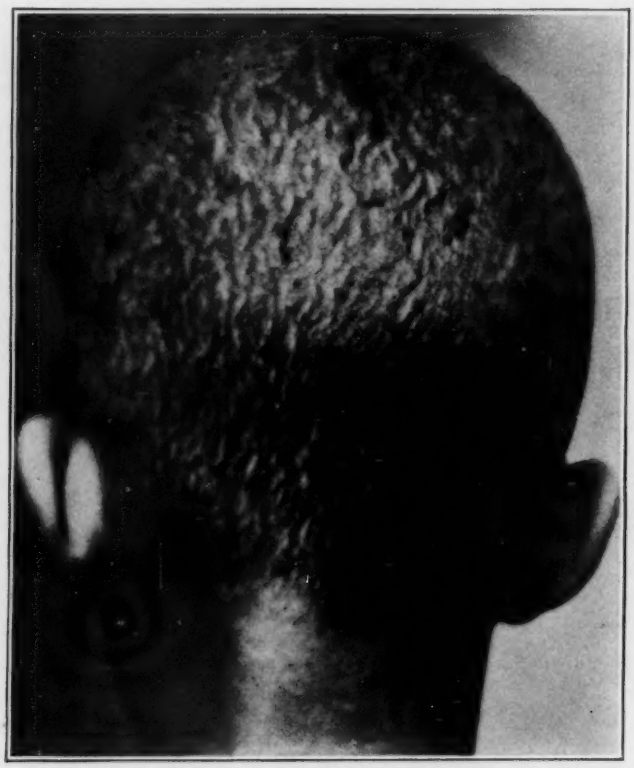

Fig. 2 (case 1).—Tinea versicolor of the scalp.

Case 2.—O. F., a white man aged 24, a Brazilian farmer, had had pityriasis versicolor on the chest and neck for eight months. On the scalp, including the entire occipital region, there were scaly macules, some of which were discrete and others confluent with no itching. Besnier's sign was positive.

Direct mycologic examination showed M. furfur in the lesions of the skin and scalp.

The reactions to trichophytin (1 : 30 solution) and oidiomycin (1 : 100 solution) tests were negative.

Case 3.—F. A. S., a Negro aged 18, born in Brazil, was a farmer. The family and personal histories were irrelevant. The patient stated that about five years

previously some spots appeared on the left side of his face; the lesions later spread to the frontal, right facial and interorbitary regions, sides of the nose, upper lip, retroauricular regions, preauricular regions, left eyelid, lobes of the ears, cheek, left facial region, scalp and trunk. Only the auricular borders and furrows and right palpebral region were spared.

All over the face there were whitish scaly macules, some of which were discrete and others of which tended to coalesce. The vertex, frontal and temporal margins of the scalp were covered with pityriasic scales. The upper part of the occipital region was spared. All the diseased parts of the scalp showed Besnier's sign.

Fig. 3 (case 3).—Tinea versicolor of the scalp. Photomicrograph showing spores and mycelium in the horny layer.

There was no itching. The lesions were for the most part diffuse. The eruption was most intense along the margin of the scalp, forming a true corona pityriasica.

On the thorax the lesions were grayish and punctiform and were situated almost exclusively at the follicular openings. All showed a positive Besnier sign.

The reactions to trichophytin (1:30 solution) and oidiomycin (1:100 solution) tests were negative.

Mycologic examination by Dr. Neves showed M. furfur in scales from the diseased scalp and glabrous parts. The hairs were not affected.

The histologic examination made by one of us showed the following picture: In a section of the hairy scalp fissures were noticed at the level of the stratum corneum, these being formed by cleavage of its layers. When this stratum was examined under high power (fig. 3) spores and hyphae were seen. The spores were not uniform in size, but the filaments were in general short and thick and sometimes interlaced, some of them showing a distinct septation. Neither spores nor hyphae reached the stratum granulosum. In the horny layer around the base of the hairs, at the level of the follicular ostiums, spores and hyphae were sometimes seen, though in our preparations these were never found in the follicular infundibula properly speaking. No change was seen in the rete malpighii, but the stratum cylindricum was deeply pigmented.

In the cutis the only change observed was a perivascular infiltration consisting of the round cells of chronic inflammation at the level of the papillary body and superficial areas of the reticular layer.

SUMMARY

We have referred to cases, recorded in world literature, of pityriasis versicolor located on different parts of the skin, making a special study of cases in which it attacked the face and scalp. We believe that the involvement of the face and scalp is favored by lack of personal hygiene and proper treatment. We present 3 cases of pityriasis versicolor of the scalp, these being the first to be recorded in Brazil.

Rua Ceará, 1695.
Rua Ourissanga, 78.

RAPID TREATMENT OF EARLY SYPHILIS

REPORT OF TWO HUNDRED AND EIGHTY TREATMENT COURSES WITH MAPHARSEN ALONE AND FIVE HUNDRED AND FORTY-NINE TREATMENT COURSES WITH MAPHARSEN COMBINED WITH FEVER

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In 1941 we made a first report [1] on the rapid treatment of early syphilis by a course of diurnal injections of mapharsen, either alone or combined with fever therapy. By June 1942 in Bellevue Hospital 829 such courses had been given. As 47 of those were retreatments of patients who either had not been cured by their first course or had been reinfected, we treated a total of 782 patients. Of these, 479 were male and 303 female, and 462 were Negroes, 283 white persons, 35 Puerto Ricans and 2 Chinese.

METHODS OF TREATMENT AND CHOICE OF PATIENTS

Originally we set out to give every patient a total of 1.2 Gm. of mapharsen. As we reported, we did not administer the drug by the intravenous drip method introduced by Chargin, Leifer and Hyman.[2] Instead, we gave 0.06 Gm. of mapharsen intravenously every morning and evening for ten days.

After thus treating 38 patients, we shortened the treatment period from ten to six days, in order to avoid an occasional "ninth day erythema." Instead of receiving 0.06 Gm. twice daily for ten days, our

This study was aided by grants from the United States Public Health Service and the American Committee on Research in Syphilis.

Miss Lena Taucci, R.N., gave invaluable assistance in the care of the patients. Dr. Henry Laven observed and followed the patients after therapy.

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1. Thomas, E. W., and Wexler, G.: Rapid Treatment of Early Syphilis with Multiple Injections of Mapharsen, Am. J. Pub. Health **31**:545 (June) 1941.

2. Chargin, L.; Leifer, W., and Hyman, H. T.: The Application of the Intravenous Drip Method to Chemotherapy as Illustrated by Massive Doses of Arsphenamine in the Treatment of Early Syphilis, J. A. M. A. **104**:878 (March 16) 1935.

patients then were given 0.1 Gm. morning and evening for six days. Thus, the dose per day was increased from 0.12 Gm. to 0.2 Gm., but the total amount of mapharsen for the course remained unchanged at 1.2 Gm.

Under this six day plan, no serious toxic reactions were seen until we were treating the one hundred and eleventh patient. This patient, a woman, died of hemorrhagic encephalitis. As the dose administered had proved harmless to all of the other patients, she evidently had a peculiar sensitivity to mapharsen. Determination of the nature, timely detection and neutralization of such sensitivity have been a major preoccupation with us. A death directly due to treatment of a not necessarily fatal disease is a tragedy to all concerned. So we set out to find the dose that would be neither great enough to endanger the abnormally sensitive nor small enough to penalize the average patient by unduly protracting his disease.

Although the investigators at Mount Sinai Hospital, New York,[3] had found that a course of mapharsen treatment with a total amount of less than 1.0 Gm. was apt to prove therapeutically disappointing, the death of our one hundred and eleventh patient led us to adopt smaller total doses. It soon became evident, however, that relapses were more frequent among patients who received less than 0.9 Gm. of mapharsen. Consequently we decided to enhance our therapy by combining fever treatments with it. This apparently did nothing to prevent rare cerebral reactions but did permit us to obtain better therapeutic results from the smaller, and hence safer, doses of mapharsen administered. Consequently we used this combined therapy in every case in which fever could do no harm.

We do not yet know the critical temperature at which fever begins to reenforce the action of mapharsen. We strove to reach 104 F. and to maintain it for four hours, which empirically we thought might be long enough to insure benefit with safety. The numbers of degree hours of effective fever given to different patients were only roughly equalized. Except for very heavy or very light patients, we did not at first attempt to adjust the dose of mapharsen to the patient's weight. Later we roughly divided the patients into categories according to their weight and correlated the dose to the category.

There are many possible combinations of fever and chemotherapy. We have attempted only a few. Our investigations have been conducted on the hypothesis that the more fever is given, the less mapharsen is required. So far our experience seems to justify this assumption. It

3. Hyman, H. T.: Clinical Considerations of Massive Arsenotherapy in Early Syphilis by the Continuous Intravenous Drip Method, Arch. Dermat. & Syph. **42**:253 (Aug.) 1940.

is possible that the treatment of early syphilis may be still further shortened and even made safer by more intensive use of fever therapy. The work of Simpson, Kendell and Rose [4] with a few patients suggests that early syphilis may possibly be cured in a single day by combining administration of arsenical drugs with ten hours of continuous artificial fever. As a rule we induced fever every other day by the intravenous injection of typhoid vaccine. This is not the most desirable means of producing fever, but in view of our heavy case load it was the most practicable method available to us. Patients vary in their reaction to typhoid vaccine. No set rule can be given as to the exact amount of vaccine required in each case. Usually we found it necessary to give two injections of vaccine in order to keep the temperature about 104 F. for at least four hours. The original dose of vaccine was 100,000,000 typhoid bacilli, repeated in about two hours. In general the amount of vaccine must be doubled on each subsequent day of fever treatment. So far we have not attempted to induce fever daily because of the discomfort this causes patients and because of our desire to evaluate the results of less heroic treatment.

In our experiments we used three different plans of combining fever with mapharsen. They are outlined as follows:

Plan 1.—Total of 0.54 Gm. of mapharsen and four fever treatments in nine days:

First day:	Two injections of 0.06 Gm. of mapharsen
Second day:	One injection of 0.06 Gm. of mapharsen and two injections of typhoid vaccine
Third day:	One injection of 0.06 Gm. of mapharsen
Fourth day:	One injection of 0.06 Gm. of mapharsen and two injections of typhoid vaccine
Fifth day:	One injection of 0.06 Gm. of mapharsen
Sixth day:	One injection of 0.06 Gm. of mapharsen and two injections of typhoid vaccine
Seventh day:	One injection of 0.06 Gm. of mapharsen
Eighth day:	One injection of 0.06 Gm. of mapharsen and two injections of typhoid vaccine
Ninth day:	One injection of 0.06 Gm. of mapharsen

Plan 2.—Total of 0.84 Gm. of mapharsen and two fever treatments in eight days:

First day:	Two injections of 0.07 Gm. of mapharsen
Second day:	Two injections of typhoid vaccine
Third day:	Two injections of 0.07 Gm. of mapharsen

4. Simpson, W. M.; Kendell, H. W., and Rose, D. L.: The Treatment of Syphilis with Artificial Fever Combined with Chemotherapy, Ven. Dis. Inform., 1942, supp. 16, p. 1.

Fourth day: Two injections of typhoid vaccine
Fifth day: Two injections of 0.07 Gm. of mapharsen
Sixth day: Two injections of 0.07 Gm. of mapharsen
Seventh day: Two injections of 0.07 Gm. of mapharsen
Eighth day: Two injections of 0.07 Gm. of mapharsen

Plan 3.—Total of 0.7 Gm. of mapharsen and three fever treatments in seven days:

First day: Two injections of 0.07 Gm. of mapharsen
Second day: One injection of 0.07 Gm. of mapharsen and two injections of typhoid vaccine
Third day: Two injections of 0.07 Gm. of mapharsen
Fourth day: One injection of 0.07 Gm. of mapharsen and two injections of typhoid vaccine
Fifth day: Two injections of 0.07 Gm. of mapharsen
Sixth day: One injection of 0.07 Gm. of mapharsen and two injections of typhoid vaccine
Seventh day: One injection of 0.07 Gm. of mapharsen

In plan 3 individual doses were given as follows: To patients under 110 pounds (50 Kg.), 0.06 Gm.; 110 to 150 pounds (50 to 68 Kg.), 0.07 Gm., and over 150 pounds, 0.08 Gm.

No patient was given rapid treatment without his or her consent, which was rarely refused. Apart from exercising great caution in treating patients with early syphilis complicated with hepatic or renal disease, we made no attempt to select our patients. Some had associated disease, such as pulmonary tuberculosis, diabetes mellitus, inactive rheumatic fever, heart disease or hypertension. There is no evidence from our experience that massive mapharsen therapy is contraindicated in the presence of pulmonary tuberculosis, but we were prejudiced against the use of fever in cases of this disease. A special report is being prepared of our experience with treating early syphilis associated with pregnancy. Suffice it to say here that we encountered no difficulty in treating by our methods of rapid therapy 14 patients with early syphilis associated with pregnancy. The use of fever for such patients does not seem harmful.

Our patients were in no sense selected. The series included practically every patient with early syphilis coming to us for treatment. Seventy-eight per cent were in the secondary stage of the disease, and some had had their infection for over one year. Of 649 spinal fluids examined before treatment, 98, or 15 per cent, gave definitely positive reactions, and 26, or 4 per cent, doubtfully positive (i. e., 4 to 5 cells with slight increases in globulin and total protein). Included in our series were 55 patients with infectious syphilis who either had had relapses

or had been reinfected after routine chemotherapy for previous early syphilis. Of these, 35 had examinations of the spinal fluid prior to the onset of treatment; 11, or 31.4 per cent, of these had positive results. Four of the 11 had symptomatic neurorecurrences with injury of a cranial nerve. Consequently our series includes patients with practically every type of early infectious syphilis and is representative of one of the most difficult sections of the population from the point of view of treatment and follow-up. We doubt if any of the reported series of patients with early syphilis treated by conventional routine methods represents a more comprehensive sample.

TABLE 1.—*Distribution of Course of Treatment by Stage of the Disease*

Total number of courses of treatment		829
Primary and secondary syphilis	690	
Primary and secondary syphilis (reinfections or relapses following previous routine therapy)	55	
Retreatments of relapses or reinfections following previous rapid treatment by the syringe method	45	
Relapses or reinfections following previous rapid treatment by the intravenous drip method	4	
Early latent and late syphilis	33	
Retreatments of late syphilis following previous rapid treatment by the syringe method	2	

TABLE 2.—*Distribution of Patients by Type of Treatment*

Total number of courses of treatment from December 1939 to June 1, 1942		829
Treated with mapharsen only	280	
Treated with mapharsen and typhoid vaccine	549	

TOXIC MANIFESTATIONS

Toxic effects of treatment with mapharsen alone and those of treatment with mapharsen and fever combined are listed in table 3. It will be seen that, with the exception of encephalitis, serious reactions are encountered no oftener with massive dosage than with routine arsenotherapy. It is probable that mild cerebral reactions are more common in the routine treatment of syphilis than is recognized, but it remains true that the chief menace of massive arsenotherapy is encephalitis. In table 3 we have listed only symptomatic reactions of the cerebrospinal axis.

Two fatalities due to treatment occurred among our patients, an incidence of 0.24 per cent for the entire series. Both patients who died received 0.84 Gm. or more of mapharsen. It is our belief that with proper caution fatal reactions to massive arsenotherapy can be reduced to a smaller fraction than that which has been reported to date. Never-

theless, the avoidance of such fatalities must remain a matter of experience as well as of chance until further knowledge of the mechanism of this strange phenomenon is obtained. We have reported elsewhere [5] our experience with cerebral reactions. In spite of the menace of the possible reactions, we believe that from a public health standpoint the advantages of rapid treatment far outweigh the risks involved, provided the treatment is given prudently. It is well known that severe encephalitis may develop after a patient has received a small amount of an

TABLE 3.—*Comparison of Toxic Effects in Patients Treated with Mapharsen Only and in Patients Treated with Mapharsen and Typhoid Vaccine*

	Mapharsen Only		Mapharsen and Typhoid Vaccine	
	Number	Per Cent	Number	Per Cent
Total courses of treatment	280	100.00	549	100.00
Herxheimer reaction or primary fever	90	32.14	178	32.42
Secondary rise in temperature	27	9.64	56	10.20
Slight elevation of temperature throughout treatment	5	1.79	2	0.36
Exfoliative dermatitis	0	0	0	0
Early acute arsenical erythema and urticaria	19	6.79	31	5.65
Pruritus (few hours' duration)	15	5.36	5	0.91
Nitritoid reaction (after tenth injection)	1	0.36	0	0
Elevation of icteric index during treatment (transient)	3	1.07	8	1.46
Jaundice (total number)	1	0.36	2	0.36
During hospitalization	0	0	1	0.18
Three weeks after treatment	0	0	1	0.18
Toxic hepatitis (cause uncertain) six months after treatment	1	0.36	0	0
Increase in blood nonprotein nitrogen during treatment (transient)	0	0	6	1.09
Hematuria (transient)	0	0	1	0.18
Blood dyscrasia	0	0	0	0
Peripheral neuritis (total number)	2	0.71	1	0.18
Within few weeks after treatment (no objective signs)	2	0.71	0	0
Immediately after treatment	0	0	1	0.18
Cerebral reaction (symptomatic)	3	1.07	7	1.28
Death (due to cerebral reactions)	1	0.36	1	0.18

arsenical drug, but in our experience the danger of serious reaction increases with the total dose of mapharsen.

The reactions encountered with the multiple injection method of treatment which we used are not appreciably different from, or more frequent than, those reported with the intravenous drip method. The use of typhoid vaccine increases the discomfort of treatment but is not in itself dangerous except under circumstances in which published experience definitely contraindicates its use.

5. Thomas, E. W.; Wexler, G., and Dattner, B.: Cerebral Reactions Associated with Massive Mapharsen Treatment of Early Syphilis, Am. J. Syph., Gonor. & Ven. Dis. **26**:529 (Sept.) 1942.

LABORATORY STUDIES

The routine laboratory studies on each patient include urinalysis, blood counts and determinations of erythrocyte sedimentation rate, nonprotein nitrogen content and icteric index. In addition to these routine procedures, special investigations were made for smaller series of patients. These include determinations of arsenic in the blood and in the spinal fluid, complete hematologic studies, with platelet and reticulocyte counts, tests of cell fragility, determination of bleeding and coagulation times and quantitative determination of bilirubin and of prothrombin. Over 600 patients had examinations of the spinal fluid before treatment was started. Of these, 250 had routine examinations of the spinal fluid after treatment and others had the examinations during or after treatment whenever we became suspicious of possible cerebral reactions. The results of our laboratory studies are being reported in separate articles. With the exception of pleocytosis and increased protein in the spinal fluid of patients with cerebral reactions, none of our laboratory investigations proved to be helpful in preventing or treating reactions of the central nervous system.

Through Dr. Wadsworth, of the New York State Health Department, Wassermann tests of the blood of most of the patients in this series were titered to the end point, the highest titer being 1,000. The advantages of this test in following the results of rapid treatment are great. A falling titer can safely be regarded as a favorable sign. When the titer rises to an appreciable degree, e. g. from 20 to 80, it is certain that the patient has had a relapse or has been reinfected. In most cases, if one looks carefully enough, infectious lesions will be found in the presence of a rising titer. In other words, our experience indicates that serologic relapse following intensive treatment for early syphilis probably means infectious relapse. In the presence of a decided rise of the Wassermann titer, we have found Spirochaeta pallida in minute erosions about the anus which would certainly have been missed on routine examination. Another common place for recurrent lesions frequently missed is the throat.

METHOD OF COMPILING STATISTICAL RESULTS OF TREATMENT

It is difficult to tabulate results of therapy in a series of patients such as we have to report. Syphilis is notorious for its refusal to conform to any set rules. Exceptions to the rule are frequent, and it becomes impossible to analyze each separate irregularity in statistical tables as a series grows. In general, the longer a patient has had syphilis, the longer it takes for a positive serologic reaction to reverse to negative, although even that rule has exceptions. Very high Wassermann titers of the blood may reverse rather rapidly, while lower titers may take a

longer time. Usually the titer falls abruptly within the first month following treatment, but as it reaches a level below 20 it may require many months for complete reversal. In most cases of secondary syphilis the serologic reaction becomes negative within six months, but in some instances it is from one to two years before no reaction whatever is found by sensitive tests.

In evaluating results it is necessary to distinquish between probable favorable and unfavorable results. Patients with Wassermann titers of the blood of less than 8 and with doubtful or negative reactions to Kahn and complement fixation tests at Bellevue Hospital are included among those with favorable results. We have every reason to believe from past experience that the serologic reactions of these patients will probably become negative. On the other hand, we have a few patients whose Wassermann titers of the blood have hovered around 20 for over six months. We have included these among patients with unfavorable results, although it is possible that their reactions too may ultimately become negative with no further treatment. Our present policy is to observe them without treatment unless other evidences of syphilitic infection develop. In the rare cases in which Wassermann titers remain over 50 for six months or more after treatment, our policy has been to retreat. Occasionally a patient disappears from observation for a number of months after finishing therapy and returns to us with a high titer. It is impossible to decide in such instances whether we are dealing with a persistently high titer, a possible relapse or a reinfection. Fortunately such patients were rare in our series. They were tabulated as having persistently seropositive syphilis.

When we compiled our tables of results of treatment all patients followed less than six months were considered lost and not included among those analyzed for probable favorable or unfavorable results, regardless of whether they had negative serologic reactions when last seen. Every patient with any evidence of serologic or infectious relapse was included among those with unfavorable results, even though the report came to us from some other city or clinic. Those who, for one reason or another, were given routine treatment elsewhere during the first six months following treatment without any evidence of serologic or infectious relapse were excluded from the analysis of therapeutic results. The remaining patients were divided into two groups: those who were still reporting to our clinic or were under observation elsewhere and those who were followed over six months but had not been heard from in the past six months. In these groups were a number of patients who were being followed or had been followed outside of the city of New York. Consequently we have included among those with unfavorable results patients whom we could not retreat ourselves but who were given routine treatment elsewhere six months or more after we treated them.

Tables 4, 5, 6 and 7 were compiled on the basis of courses of treatment. In other words, we analyzed the results of each course of treatment separately. Thus, when a patient was retreated by one of our methods the first course of treatment was listed as a failure and the retreatment was counted as a new course. If the patient still had a Wassermann titer of the blood of greater than 8 six months or more

TABLE 4.—*Status of One Hundred and Fifty-One Patients Six to Twenty-Nine Months After Treatment with 0.9 to 1.2 Gm. of Mapharsen*

	Sero-negative Primary Syphilis	Sero-positive Primary Syphilis	Secondary Syphilis	Total Number	Total Per Cent	
Status of patients followed 6 to 29 months						
Lost (followed less than 6 mo.)	5	6	25	36	23.84	
Lost (routine treatment)*	0	0	4	4	2.65	
Number followed 6 to 29 mo	2	24	85	111	73.51	
Total number treated	7	30	114	151	100.00	
Probable favorable results						
Negative serologic reactions (followed 8 to 29 mo.)†	0	17	55	72	64.86	
Negative serologic reactions (followed 6 to 20 mo. but not examined in past 6 mo.)‡	1	4	14	19	17.12	
Wassermann titers less than 8§ (followed 14 to 21 mo.)	0	1	1	2	1.80	
Probable favorable results (total number	1	22	70	93		83.78
Unfavorable results						
Relapse or reinfection	1	2	7	10	9.01	
Wassermann titers greater than 10 (followed 11 to 23 mo.)†	0	0	6	6	5.41	
Wassermann titers greater than 10 (followed 7 to 9 mo. but not examined in past 6 mo.)‡	0	0	2	2	1.80	
Unfavorable results (total number)	1	2	15	18		16.22
Total number followed	2	24	85	111	100.00	100.00

* For these patients, routine treatment was started elsewhere within five months after receiving rapid therapy. There were no relapses in this group.

† These patients are under observation, having been examined in the period between Dec. 1, 1941 and June 1, 1942.

‡ These patients were last examined before Dec. 1, 1941.

§ These patients now have Wassermann titers (New York State Department of Health) in the range between 3 and 8. Prior to treatment the titers of this group ranged between 100 and 1,000. The Wassermann test at Bellevue Hospital in most of these cases has given completely negative reactions. Our experience indicates that the serologic reactions of this group will probably become completely negative.

after the second course of therapy he was again counted among those with unfavorable results, or if his titer was less than 8, among those with probable favorable results.

STATISTICAL ANALYSIS OF RESULTS OF COURSES OF TREATMENT

For statistical purposes, patients receiving mapharsen alone were divided into two groups, table 4 dealing with those who received over 0.9 Gm. of mapharsen and table 5 with those who received less than

0.9 Gm. It should be stated that the great majority of patients listed in table 4 received over 1.0 Gm. of mapharsen. This group is practically the same as the one reported on last year, with a few additional patients who received 0.9 Gm. of mapharsen. At the time of our last report we had a total of 142 courses of treatment, 95 of the patients having been followed for over six months. The percentage of probable favorable results was 86.3. This year, with a total of 152 courses of treatment and 111 of the patients followed for over six months, the incidence of

TABLE 5.—*Status of One Hundred and Twenty-Two Patients Six to Twenty-Five Months After Treatment with 0.66 to 0.84 Gm. of Mapharsen*

	Sero-negative Primary Syphilis	Sero-positive Primary Syphilis	Secondary Syphilis	Total		
				Number	Per Cent	
Status of patients followed 6 to 25 months						
Lost (followed less than 6 mo.)	1	4	25	30	24.59	
Number followed 6 to 25 mo	3	12	77	92	75.41	
Total number treated	4	16	102	122	100.00	
Probable favorable results						
Negative serologic reactions (followed 12 to 25 mo.)	2	8	45	55	59.78	
Negative serologic reactions (followed 6 to 14 mo. but not examined in past 6 mo.)	0	0	10	10	10.87	
Wassermann titers less than 8 (followed 21 to 23 mo.)	0	0	2	2	2.17	
Wassermann titers less than 8 (followed 6 to 8 mo. but not examined in past 6 mo.)	0	0	2	2	2.17	
Probable favorable results (total number)	2	8	59	69		74.99
Unfavorable results						
Relapse or reinfection	1	4	16	21	22.83	
Wassermann titers greater than 10 (followed 6 to 23 mo.)	0	0	2	2	2.17	
Unfavorable results (total number)	1	4	18	23		25.01
Total number followed	3	12	77	92	100.00	100.00

probable favorable results is 83.78 per cent. The difference in percentages is not due to additonal serologic or infectious relapses, because the proportion of these remain exactly the same as in our first report of over a year ago. The 3 per cent difference in percentage is not considered significant, because 1 or 2 of the patients listed as having positive serologic reactions may still come to have negative reactions and several patients included last year among those lost from observation were later reported by other clinics as having been given routine treatment.

In the group receiving less than 0.9 Gm. of mapharsen the percentage of favorable results was only 75 per cent, a significantly poorer result than with the higher dosage. The same was true in our report of last

year, when we listed 76 per cent of this group as having probable favorable results.

It must be admitted that our grouping of patients is somewhat arbitrary, because it is not based on a definite amount of drug per kilogram of body weight. The determining factor in the unfavorable cases, however, cannot be related to differences in weight. In other words, failures with the same dosage of mapharsen occurred as fre-

TABLE 6.—*Status of One Hundred and Twenty-Eight Patients Six to Nineteen Months After Treatment with 0.54 to 0.6 Gm. of Mapharsen Combined with Four Sessions of Fever Induced by Typhoid Vaccine*

	Sero-negative Primary Syphilis	Sero-positive Primary Syphilis	Secondary Syphilis	Total		
				Number	Per Cent	
Status of patients followed 6 to 19 months						
Lost (followed less than 6 mo.)	1	9	20	30	23.44	
Lost (routine treatment)	0	0	2	2	1.56	
Number followed 6 to 19 mo.	5	7	84	96	75.00	
Total number treated	6	16	106	128	100.00	
Probable favorable results						
Negative serologic reactions (followed 7 to 19 mo.)	4	6	63	73	76.04	
Negative serologic reactions (followed 7 to 19 mo. but not seen in past 6 mo.)	0	0	3	3	3.13	
Wassermann titers less than 8 (followed 9 to 17 mo.)	0	0	4	4	4.16	
Wassermann titers less than 8 (fol- 8 to 9 mo. but not seen in past 6 mo.)	0	0	3	3	3.13	
Probable favorable results (total number)	4	6	73	83		86.46
Unfavorable results						
Relapse or reinfection	1	1	7	9	9.38	
Wassermann titers greater than 10 (followed 12 mo.)	0	0	2	2	2.08	
Wassermann titers greater than 10 (followed 6 to 8 mo. but not seen in past 6 mo.)	0	0	2	2	2.08	
Unfavorable results (total number)	1	1	11	13		13.54
Total number followed	5	7	84	96	100.00	100.00

quently among patients who weighed less than 140 pounds (63.5 Kg.) as among those who weighed over 140 pounds. Thus, regardless of weight, the results of treatment with 0.9 Gm. or more of mapharsen alone were definitely better than with smaller total doses.

The patients who received combined mapharsen and fever therapy were divided into two groups. In table 6 are analyzed courses of four fever treatments and not over 0.6 Gm. of mapharsen, the great majority of patients receiving only 0.54 Gm. of mapharsen. The percentage of 86.46 for probable favorable results in this group is significantly greater than in the group that received less than 0.9 Gm. of mapharsen without

fever (table 5). There is no significant difference between the group in table 6 and that in table 7, in which two or three fever treatments and from 0.7 Gm. to 0.84 Gm. of mapharsen were given to each patient. Such difference as there is between these groups favors four fever treatments and a smaller amount of the drug.

If patients not seen in the past six months are excluded from our analysis of results of treatment, the percentages of favorable and unfavorable results remain practically the same. In fact, the percentage of favorable results of one course of treatment with combined fever

TABLE 7.—*Status of One Hundred and Seventy-One Patients Six to Fifteen Months After Treatment with 0.7 to 0.84 Gm. of Mapharsen Combined with Two to Three Sessions of Fever Induced by Typhoid Vaccine*

	Sero-negative Primary Syphilis	Sero-positive Primary Syphilis	Secondary Syphilis	Total		
				Number	Per Cent	
Status of patients followed 6 to 15 months						
Lost (followed less than 6 mo.)	2	8	29	39	22.81	
Lost (routine treatment)	0	0	1	1	0.58	
Number followed 6 to 15 mo	13	21	97	131	76.61	
Total number treated	15	29	127	171	100.00	
Probable favorable results						
Negative serologic reactions (followed 6 to 15 mo.)	12	19	65	96	73.28	
Negative serologic reactions (followed 6 mo. but not examined in past 6 mo.)	1	0	1	2	1.53	
Wassermann titers less than 8 (followed 7 to 14 mo.)	0	0	13	13	9.92	
Wassermann titers less than 8 (followed 11 mo. but not examined in past 6 mo.)	0	0	1	1	0.76	
Probable favorable results (total number)	13	19	80	112		85.49
Unfavorable results						
Relapse or reinfection	0	1	10	11	8.40	
Wassermann titers greater than 10 (followed 6 to 15 mo.)	0	1	7	8	6.11	
Unfavorable results (total number)	0	2	17	19		14.51
Total number followed	13	21	97	131	100.00	100.00

and mapharsen or with 1.0 Gm. or more of mapharsen alone is about 85 per cent by every possible method of compiling statistics of the facts now available to us. If we separate patients with primary syphilis having negative serologic reactions, patients with primary syphilis having positive serologic reactions and patients with secondary syphilis in the more adequately treated groups, we have the following probable favorable results: 90 per cent, 90.4 per cent and 83.8 per cent respectively. These percentages are based on a single course of treatment. A summary

of probable favorable results, including retreatments, is found in table 8. This shows 89.4 per cent probable favorable results for the entire series of patients followed over six months.

Table 9 gives the results of examinations of spinal fluid made from six months to two years after treatment. It is a striking fact that spinal fluids examined from six to twenty-eight months after treatment, with a single exception, were normal. The exception is explained in the

TABLE 8.—*Summary of All Patients Followed Six to Twenty-Nine Months After Treatment*

	Favorable Results Expressed in per Cent			
	Sero-negative Primary Syphilis	Sero-positive Primary Syphilis	Secondary Syphilis	Total
Results of 430 treatment courses (each retreatment considered a new case)	86.9	85.9	82.2	83.0
Results in 404 patients after 1 course of treatment (retreatments omitted)	85.0	85.2	82.7	83.2
Results in 404 patients (retreatments included)	100.0	90.0	88.5	89.4
Results in 314 patients who received more adequate treatment (tables 4, 6 and 7 with retreatments included)	100.0	91.8	89.5	90.4

TABLE 9.—*Results of Examination of Spinal Fluid Six to Twenty-Eight Months After Treatment*

	Treated with Mapharsen Only	Treated with Mapharsen and Fever	Total
Patients with negative reactions of spinal fluid	136	167	303*
Patients with positive reactions of spinal fluid	0	1†	1
Total number of patients examined	136	168	304‡

* Thirty-eight of these patients had spinal fluids with positive reactions before treatment.
† This patient had recurrent secondary syphilis with strongly positive reactions of the spinal fluid before treatment. Thirteen months after treatment the examination of the spinal fluid revealed a 4 plus Wassermann reaction, 4 white blood cells, a faint trace Pandy reaction, 20 mg. total protein per hundred cubic centimeters and a negative colloidal gold reaction.
‡ Forty-six of these patients have had two or more examinations of the spinal fluid twelve to eighteen months apart.

footnote of table 9. We are not retreating this patient because of her well-being and the fact that her spinal fluid is much improved without further therapy. We believe that it will probably become normal in time without additional treatment. The Wassermann titer of her blood, which was 190 before her last treatment, has fallen to 21, thirteen months later.

COMPARISON OF RESULTS WITH THOSE OF ROUTINE TREATMENT

It is difficult to find a comparable series of patients with early syphilis treated by adequate therapy with conventional methods. The

reports of the Cooperative Clinic Group [6] in this country are the most reliable that we have found. Of 167 patients who were given more than one year of continuous routine therapy by the Cooperative Clinic Group, 9 per cent had relapses or resistant serologic reactions. Of 620 patients treated irregularly for one year or more, 43.5 per cent had relapses or resistant serologic reactions. When retreatments are considered, our results therefore compare favorably with those of the best conventional routine treatment. Furthermore, it is well known that only a small percentage of clinic patients in this country persist in continuous routine treatment for six months. This fact alone demands continued efforts to find quick and relatively safe methods of treating early syphilis.

RELAPSES AND REINFECTIONS

It was found both by the Cooperative Clinic Group and by us that relapses occur more frequently among Negroes than white persons and among males than females. The percentage of relapses among Negroes in our group is twice that among white persons. As Negroes far outnumber the white patients in our series, this fact is of importance.

Most of our unfavorable results fall in the group of relapses or reinfections. From our case records there is ample evidence that some patients had reinfections. In fact, most of the patients in this group admitted repeated promiscuous sexual intercourse, some with persons known to have syphilis. Seven patients had intercourse with the same sexual partner after treatment and returned to us with new infectious lesions. For 6 of these we found and treated the probable source of the second infection.

Nevertheless, analysis of our statistics favors the diagnosis of relapse rather than of reinfection. Of the 51 patients listed as having relapses or reinfections, 44, or 86 per cent, had the condition discovered within the first six months after treatment. Of the remaining 7, all but 1 lapsed from our follow-up and seven to ten months after treatment were found to have infectious lesions of uncertain duration. The serologic reactions of the other patient became negative four months after treatment and remained so until the eighth month, when a lesion in which spirochetes could be detected by dark field examination developed about the anus and the Wassermann reaction of his blood again became positive. Thus, in our series relapse or reinfection was rarely observed over six months after treatment, and we must assume that if the conditions noted were reinfections the patients were reinfected in the first six months or seldom thereafter. Inasmuch as there is no reason to believe that the incidence of exposures to new infections varies over several years, the high per-

6. Cooperative Clinical Studies in the Treatment of Syphilis: III. Results of Treatment in Early Syphilis, Ven. Dis. Inform. **13**:253 (July 20) 1932.

centage of new infectious lesions during the first six months following treatment favors relapse. Furthermore, such additional statistical evidence as exists in our study favors relapse rather than reinfection. In the three more adequately treated groups the percentages of relapses and of reinfections were practically identical (9.0 per cent). In the group receiving less adequate therapy (table 5) there were 22.84 per cent relapses or reinfections.

At the time of relapse or reinfection, 44 patients originally treated by us had examinations of the spinal fluid; the fluids of 37, or 84 per cent, were normal and those of 7, or 16 per cent, gave positive reactions. One patient had a symptomatic neurorecurrence but the spinal fluid was normal six months after retreatment. Thirty-two of these patients have been followed for over six months since retreatment. Three, or 9.3 per cent, showed relapse or were reinfected for the second time. Eighteen have negative serologic reactions at present; 7 have Wassermann titers of the blood of less than 8 and 4 still have positive reactions. Thus, at least 78.2 per cent of the retreated patients are now in the group with favorable results. Seventeen had examinations of the spinal fluid over six months after retreatment. The fluids of all except the 1 patient already mentioned were normal. Of all the patients treated for relapse or reinfection following either routine or intensive therapy by the intravenous drip method or by our method, 57 have been followed for over six months. Of these, 48, or 84.2 per cent, have favorable results.

EARLY LATENT SYPHILIS

Ten patients with early latent syphilis of four to twelve months' duration, who were given rapid courses of treatment with 1.0 Gm. or more of mapharsen or with fever combined with mapharsen, were followed from seven to twenty-five months. Four had no previous antisyphilitic treatment. One was in the latent stage after having previously had a relapse following routine treatment. Five patients had one to six months of previous routine treatment. At the time of writing, 6 of the 10 have negative serologic reactions and 3 have Wassermann titers of the blood below 8—a total of 90 per cent probable favorable results. Eight had examinations of the spinal fluid seven to sixteen months after treatment, and the fluids of all these were normal.

COMMENT

More time must elapse before the results of our therapy can be properly evaluated, but we believe that the prospect of permanent cure in our favorable cases is good. The possibilities for the rapid treatment of early syphilis are by no means exhausted. It is probable that further investigations in this field will yield better and more successful methods

than have been reported to date. Because of our desire to evaluate results with a single course of treatment in fairly large series of patients, we have refrained from complicating our investigations with any additional routine therapy after the patients left the hospital. If this were done, it is possible that the number of relapses could be greatly reduced.

CONCLUSIONS

1. Massive doses of mapharsen can be given satisfactorily in multiple injections without resorting to the intravenous drip method.

2. The risk of serious cerebral reactions increases with the amount of mapharsen given.

3. The therapeutic results obtained with a total dose of less than 1.0 Gm. of mapharsen alone in a period of six days of treatment are definitely less satisfactory than with a total dosage of 1.0 Gm. or more.

4. The combination of fever, induced by typhoid vaccines, with massive mapharsen therapy does not prevent cerebral reactions but lessens their danger by permitting a much smaller total dosage of mapharsen without loss of therapeutic effectiveness.

5. The present status of significantly large series of patients with early syphilis treated rapidly with either a total dosage of 1.0 Gm. or more of mapharsen or with a combination of fever and less than 0.9 Gm. of mapharsen compares favorably with the results of prolonged continuous routine treatment.

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EVALUATION OF A FUNGICIDAL AGENT FOR FUNGOUS DISEASE OF THE FEET

A CONTROLLED HOSPITAL STUDY

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This report is presented to show some of the difficulties encountered in attempting a controlled clinical study of a fungicidal agent. It is always difficult to determine, in a relatively short period, the true value of therapeutic agents for the treatment of fungous disease of the feet. The analysis is made usually by pure clinical observation, by laboratory findings or, what is more common, by a combined clinical and laboratory survey. Many of these studies are open to criticism because of the duration of the period of observation, lack of controls and lack of continued observation of patients during the test period.

In an effort to work out a controlled program for the study of a fungicide in the therapy of fungous infection of the feet the following plan was adopted: (1) continued hospital observation of the patient by different observers in different institutions; (2) use of one foot as control, and (3) laboratory studies before, during and after therapy.

An accurate and detailed chart was kept of the patient's condition, including a description of the extent and severity of lesions, laboratory data and also critical opinions of the results of therapy. Therapy was applied daily, only by medical or nursing personnel. The control foot was treated only with the vehicle of the medicament which was used on the treated foot of the same patient. The degree of involvement of

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Grant for the study was given by the Hamilton Laboratories, Inc.

From the Department of Dermatology and Syphilology and the Department of Bacteriology, University of Cincinnati College of Medicine, and the Cincinnati General Hospital.

The study was done under the direction of Dr. Harry Claassen, Director Department of Dermatology and Syphilology, and Dr. Lee Foshay, Director Department of Bacteriology.

the control foot was also recorded in detail. Laboratory studies included trichophytin tests (made only once during the study of the patient), scrapings and cultures. In some instances special cultures were made for associated local pyogenic organisms, and some patients were tested by vaccines made from these organisms. In addition, the study included cutaneous patch tests with varying concentrations of the agents. The project was carried out in the dermatologic wards of the Cincinnati General Hospital, the Hamilton County Home and Chronic Disease Hospital, the Longview State Hospital and the Quarantine Hospital of the Cincinnati Workhouse.

The most obvious objection to such a study for the clinical evaluation of therapy for fungous disease of the feet was that the environment of rest in bed in a hospital was an artificial one and not similar to actual conditions under which the infection is usually acquired or aggravated or treated. However, as aforementioned, it is not possible to observe outpatients critically and frequently. Some few of the patients included in this series were institutional ones who were up and about. There was a minimum of two weeks' observation of the patient, but most of the patients were observed for much longer periods.

The fungicides selected for study were phenylmercuric nitrate (basic) and phenylmercuric borate. These materials have been used for some time and have been reported on extensively in the literature. They were used in the following ways:

1. Phenylmercuric borate cream 1 : 500 with 1 per cent boric acid in a vanishing cream base.
2. Phenylmercuric nitrate (basic) ointment 1 : 1,500 with an oxycholesterol base and 0.1 per cent boric acid.
3. Tincture 1 : 500 phenylmercuric borate 0.2 per cent in an acetone, alcohol, aqueous solution.
4. Solution 1 : 500 phenylmercuric borate, Triton NE, wetting agent combination.
5. Constant wet dressings with 1 : 25,000 solution plus a small amount of sodium chloride.
6. Constant wet dressings with 1 : 25,000 tincture plus a small amount of sodium chloride.

In each case only the vehicle of the respective combination was used on the control foot. There was no control as regards comparative efficacy with other fungicidal materials. The outline of the study had been approved in advance by the Council on Pharmacy and Chemistry of the American Medical Association. The results are given in the accompanying tables.

A study of controlled hospital observation of fungous disease of the feet seemed simple to organize and to interpret from a theoretic

aspect but was actually difficult to work out and to analyze. Some confusing factors were: (1) minimum time (two weeks) of observation (however, no fungicide which does not cause improvement in two weeks of correct application should continue to be used), (2) spontaneous

TABLE 1.—*Summary of Results*

Total number of patients	114
Cured	18
Improved	84
Not improved	12
Control improved	34
Trichophytin	
Positive	78
Negative	31
Cultures	
Positive	25
Negative	85

TABLE 2.—*Influences of the Form of Local Treatment*

Medication	Helped	Not Improved	Control Improved
Cream	57	5	18
Ointment	16	2	9
Tincture	19	4	3
Solution	10	1	4
Total	102	12	34

TABLE 3.—*Analyses of Scrapings and Cultures*

	Before Treatment (114 Patients)		After Treatment (51 Patients)	
	Active Foot	Control Foot	Active Foot	Control Foot
Scrapings				
Positive	27	24	2	10
Negative	87	90	49	41
Cultures				
Positive	22	15	3	7
Negative	92	99	47	43

improvement of the control foot in 34 instances with the patient at rest in bed (in such instances, however, the treated foot improved also) and (3) the fact that rest in bed in a hospital is not the usual environment in which a fungous disease of the feet relapses.

There are some criticisms in regard to the type of fungous disease studied. Since the study was made in the fall, winter and early spring, the low grade scaling form was the one usually observed. Only 11 of

the 114 patients presented the acute vesiculopustular form. The chronic asymptomatic scaling type is, however, the most frequent type of fungous disease of feet. If this type can be treated successfully, a valuable advance in the difficult prophylactic program against fungous diseases will be accomplished. The study showed these phenylmercuric compounds to be of value.

A relatively small number of initial positive results of scrapings and cultures was obtained. This suggests that some of the conditions clinically diagnosed as fungous infections may not have been such. In practice, however, the diagnosis is made in most instances by the clinical appearance alone. It is our impression that in this "quiescent" form of fungous disease, so common during the season studied, scrapings and cultures show a lesser number of positive results.

Moreover, a study of the control foot showed that scrapings and cultures may become negative spontaneously. There was an unusually

TABLE 4.—*Results of Patch Tests*

Medication	Positive Reaction	Negative Reaction
Cream	8	25
Ointment	2	31
Solution	10	2
Tincture	10	1
1:25,000 solution	0	18
1:25,000 tincture	0	18
Wetting agent	0	33

small number of positive laboratory findings. However, the series was large enough to show significantly greater degrees of improvement of the treated feet. When these results are added to the improvement (spontaneous) of the control foot, the summation shows a considerable amount of improvement.

Several other parts of the study were not of great value because the series of cases was too small. These include the important phases of local prophylaxis under continued supervision and the study of the importance of associated pyogenic organisms.

It is recognized, of course, that it is difficult to establish a cure of fungous disease of the feet. We did not consider a patient as cured unless certain definite requirements were fulfilled. First, he must have had definite clinical and laboratory evidence of fungous disease before treatment had been started. Next, he must have remained normal clinically and bacteriologically, under observation, for an "appreciable length of time," at least more than four to six weeks under therapy. Third, he must have maintained this normal condition for some weeks after all therapy had been discontinued. With those rigid but obvious restrictions only 18 patients were considered as cured.

An attempt was made to study the value of the aforementioned materials as prophylactic agents. This was done by using the agents on a group of noninfected persons who were exposed to working conditions in one of the institutions (the workhouse) where fungous infection of the feet was prevalent. Approximately 50 per cent of the persons working in a certain section were apt to have such infections. The series was too small (12 cases) for one to draw any conclusions.

To complete the clinical study of the fungicide, its potential cutaneous irritant qualities were determined by observation of the reactions occurring during therapy and by patch tests. These patients were not examined to determine if there was a sensitivity to mercury. There were a considerable number of positive reactions to patch tests in the concentrations listed. The warning on the label of the medication is therefore justified. However, in actual practice, only 2 patients in the entire series of 114 had a dermatitis from the preparation. This demonstrated that the agent is a potential irritant if used incorrectly, i. e. if bandaged. When the material was used as recommended the irritation was observed in less than 2 per cent of the cases.

SUMMARY AND CONCLUSIONS

An ideal clinical study of a fungicidal agent for fungous disease of the feet should include a preliminary toxicologic investigation and then the observation of its effect on the sites of proved infection with controlled areas untreated. The environment should be similar to that offered in actual practice. The study should then include also the value of this material as a local prophylactic agent. In addition, there should be a detailed examination of its cutaneous irritant properties.

In an attempt to duplicate the clinical phases of this scheme with a controlled hospital study of the effect of phenylmercuric salts, it was revealed that only a moderate scaling chronic form of this disease was found (103 out of 114 cases) or at least diagnosed clinically at the time of year during which the study was made, September to May. It was demonstrated that scrapings and cultures may become negative spontaneously, without therapy, and also that fungous disease of the feet may improve spontaneously under rest in bed. Because of this tendency of the control foot to show such spontaneous improvement, confusion in interpretation of data may arise. In each instance the treated foot improved also.

The series was large enough to substantiate the claims that phenylmercuric compounds are active fungicides. Under the recommended mode of application these drugs showed only about 2 per cent irritating quality.

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"RED MOSS" DERMATITIS

CONTACT WITH SPONGES AFFECTING OYSTERMEN

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The book on occupational diseases of the skin, by Schwartz and Tulipan,[1] contains a somewhat brief comment on various dermatoses which stem from work involving contact with sea life. Among these the vocation of oyster dredging and handling is not categorically mentioned. Of the diseases produced, erysipeloid (Rosenbach) and miscellaneous dermatoses of marine workers receive due attention as hazards of the fish and shellfish business. "The Fish Industry" is the heading of a section of the book which includes dermatoses derived from contact with various sea forms, most of them being free swimmers. Mention is made, however, of sponge fishers who are often stung by an anemone, a parasite on sponges. This sting is followed by immediate erythema and by blisters which develop within a few minutes. Evidently the primary irritant is of a severe nature, as in some cases multiple abscesses, sloughing and exfoliation of the skin occur.[2] Quarelli [3] has said that old sponge fishermen bear numerous scars from former attacks of dermatitis caused by small sea anemones. The only note found relative to oyster handlers is the mention of keratitis believed due to shell fragments which lodge in the eye during the process of opening the shells.

The following case illustrates an additional type of occupational hazard for oystermen.

REPORT OF A CASE

R. C., a white man aged 38, married, a resident of Port Norris, N. J., a Delaware Bay town, was engaged in oyster dredging as a part time (seasonal) occupation. He was first seen by us on Feb. 4, 1942, referred by Dr. Sherman A. Eger, of Philadelphia, for an eruption on both hands, which, he announced, was "red moss poisoning." He said that oyster workers were occasionally afflicted with this disease and that they had much trouble getting rid of it.

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1. Schwartz, L., and Tulipan, L.: A Text-Book of Occupational Diseases of the Skin, Philadelphia, Lea & Febiger, 1939.

2. Zervos, S. G.: La maladie des pêcheurs d'éponges nus, Paris méd. **2**:89, 1934; La maladie des pêcheurs d'éponges nus et l'anímone de la mer "actinion," Bull. Acad. de méd., Paris **119**:379, 1938.

3. Quarelli, G.: Professional Diseases of Fishermen, Minerva med. **22**:177, 1931.

His previous history was without significance, the only eruption he recalled being one on the feet, which by description suggested dermatophytosis. No other member of his family was affected with any disease of the skin.

On the evening of Oct. 4, 1941, after a day's labor on the bay, the fingers of his left hand suddenly became uncomfortably stiff and red. The next day blisters filled with a clear liquid were noted to have formed on his fingers and there was a painful sensation, as though his hand had been burned. Three days later the right hand became similarly involved. Some of the blebs later showed purulent contents. There were no subjective symptoms aside from the local discomfort and inconvenience. The outbreak was intractable and persisted through the winter season, possibly adversely influenced by treatment consisting largely of the use of local antiseptics, principally diluted solution of sodium hypochlorite U. S. P. and potassium permanganate. Some roughness between the toes and on the soles was noticed by him two months after the eruption on the hand appeared.

When first seen by us the patient had protected his hands, which were very sensitive, by muslin bags pinned to his coat sleeves. The skin was mahogany colored and leathery owing to the permanganate soaks. This toughened epidermis covered vesicles varying in size from that of a pinhead to that of a pea, and the hands were swollen, the fingers tense and glazed. The eruption did not extend above the wrists.

The patient was in the Jefferson Hospital for study from Feb. 7 to 10, 1942. He furnished fresh samples of a spongelike material which he said was the causative "red moss." A patch test on the flexor surface of the forearm produced in eight hours a positive reaction, an area of itchy redness of a shape corresponding to that of the material being tested. This area faded in about a week, although a stain remained for over a month.

The results of general physical examination were practically normal. Many of his teeth were missing, and the majority of those remaining showed amalgam fillings. His tonsils were small and the pharynx red. There was no enlargement of the thyroid. There was moderate axillary and epitrochlear lymphadenopathy.

The patient's hands were softened with bland ointments and soaked to remove the permanganate-stained integument. The vesiculation and swelling gradually subsided, and by late April the affected regions were practically normal save for an occasional outbreak of small vesicles on the pads of the left index and middle fingers. On February 20 the feet showed some interdigital irritation, which gradually disappeared.

The laboratory studies included an examination of the blood, showing 94 per cent hemoglobin, 5,400,000 red blood cells, 13,200 white blood cells and a color index of 0.8. The differential count showed neutrophils 53 per cent, young forms 6 per cent, eosinophils 7 per cent, monocytes 1 per cent and lymphocytes 33 per cent. The urine was acid with a specific gravity of 1.018. There was a light cloud of albumin but no sugar. The microscopic observations were normal. Scrapings from the hands and feet showed no fungi at any time. Permission to perform a biopsy was refused.

"Red moss," or, more properly, red or red beard sponge, is a submarine growth of shallow waters resulting from the attachment of a budlike immature form to some submerged object. It differs somewhat in appearance, but as a rule when well developed (this description is based on growths furnished by the patient) it appears as a thick,

firm, elastic body with papillary projections which are most noticeable on the distal portions, where it forms relatively thick finger-like subdivisions. In some cases the growth is almost exclusively composed of the latter features. A plate of attachment to some object served as the base for thin, rust-colored branches some 3 to 7 inches (7.5 to 18 cm.) in length in the specimens furnished by a New Jersey official charged with supervision of the oyster beds in that district. The surface is rough and granular in a dried state, slightly crackly and comparable to the common understanding of what the term sponge should suggest. When wet the surface feels fuzzy. The reddish color is found for the most part at the sides of the thicker form of growth and varies in intensity, usually being of a russet or brownish red shade when dried and brighter in hue when water soaked.

The patient observed that it was more common to find the spongy growths in the new beds, where seed oysters had been planted, and when

Fig. 1.—Red moss (one-third natural size).

dredging was in progress, breaking up the new growth for the first time. The moss is not necessarily attached to the oyster shells but is growing on the bottom and, loosened by the dredger, is brought up in quantities and must be sorted out and thrown overboard. The workers wear rubber gloves in winter but in summer employ finger stalls for protection. These are loose and permit debris to enter them and must be frequently emptied out. The weather was warm when our patient's eruption began, and stalls were being used by the workers.

Mr. Richard A. McLean, of the Academy of Natural Sciences, Philadelphia, crushed some of the material forming the outer layer of the sponge, demonstrated the siliceous spicules which were found in that region and identified the growth as Microciona prolifera. These spicules were for the most part needle-like bodies with a beveled point of great sharpness. In length they varied from a few to as much as 500 microns, while in breadth they differed from 6 to 15 microns. Some variations

included bulbous tips to the needles and so-called "toxas," cupid's bow-shaped forms.

In the absence of any knowledge of poisonous principles or infectious agents contained in or around these needles, it might be assumed that the spicules themselves produce trauma by abrasion or puncture and might even become detached from the sponge and enter the skin, causing a foreign body reaction.

Szentkiralyi,[4] in searching for the cause of a dermatitis afflicting wading fishermen in the Tisza valley, discovered a foreign body in a

Fig. 2.—Siliceous spicules (× 150).

biopsy section. This was a fine, pointed, transparent structure projecting into the upper layers of the epidermis. He described the section as follows:

> The section showed only an edema of the cutis with dilatation of the vessels. Apparently there had not been sufficient time for development of any decided inflammation. Closer examination revealed that this foreign body was a frag-

4. Szentkiralyi, S.: Ueber eine durch Süsswasserschwämme verursachte Hauterkrankung des Tisza- (Theiss-) Fischer, Dermat. Wchnschr. **104**:602, 1937.

ment of the thorn of a fresh water sponge. The skeleton of the sponge consists of spicules of calcium and silicic acid arranged in longitudinal bundles and held together with spongin. The individual spicules are pointed at each end.

The same writer alluded to a case reported by Kurt Lambert in which a man mistook a colony of such sponges for a real sponge and washed himself with it, receiving a severe inflammation of the skin. Györffy [5] spoke of a zoologist who was collecting sponges and, while thus occupied, scratched his neck and produced a dermatitis. Entz and Sebess [6] stated that fishermen and bathers in the Balaton Lake frequently developed a rash which was clearly due to spicules. The reason for this conclusion was not given.

The condition in our case was of such long duration (four months) when first seen that it seemed illogical to expect to find such bodies in the skin, even had a biopsy been performed. Bodily activities would give rise to a certain amount of mechanical friction which would take place between the tested material and the skin in contact. Using the material mentioned with the spicules present separated from the softer parts of the sponge (this was accomplished by boiling the sponge in nitric acid and separating the spicules by washing and filtration), we again (July 1942) obtained a positive though less impressive reaction to a patch test on the patient's arm. This would seem to indicate that a mechanical irritant rather than allergy was responsible for the inflammation. The difference in degree of response to the patch tests, contrasting the use of whole tissue of the sponge to the spicule emulsion on lint, is possibly due to the fact that in the former the spicules are more largely embedded at right angles to the surface of the skin and consequently produce a more strongly abrasive effect than is the case when the spicules are loosely applied. A patch test with the protein extract of the growth free of spicules gave negative results.

Dr. Henry B. Decker called our attention to the mention of "sea strawberries" from a "strawberry bottom" in "Captains Courageous," Kipling's story of life on the Grand Banks. These sea nettles (suggested by their effects when grasped) might possibly be related to the "red moss" of more southerly waters.

About the time this patient had his dermatosis, 5 other men, he said, were similarly affected in varying degrees. Dr. Charles E. Sharp, of Port Norris, N. J., wrote us of his experience with the disease. He said:

I have seen a great many cases of red moss poisoning, some seasons many more than others. Most of them begin along the sides of the fingers, later involving the entire finger and sometimes spreading to the hand. Usually more than one finger is affected.

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5. Györffy, cited by Szentkiralyi.[4]
6. Entz and Sebess, cited by Szentkiralyi.[4]

Dr. Thurlow C. Nelson,[7] in a paragraph entitled "Skin Irritation Due to Red Beard Sponge," wrote:

> The handlers of oysters in Maurice River Cove reported during the autumn of 1928 considerable irritation and soreness of the hands due to the "red beard" sponge, Microciona, which was attached in abundance to the oysters. The source of the irritation, evidently the spicules, was found to pass readily through the heavy cloth gloves employed by the men. Experiments are now in progress with a view to obtaining if possible a glove which will be impervious to the source of irritation.

In a personal communication the same writer said:

> The only gloves I know of which might prevent the irritation are those made of sharkskin and worn by oystermen on the Pacific Coast when handling very sharp oysters. Rubber gloves might do for a short time, but in the type sold to our oyster handlers cracks develop in a few days.

CONCLUSION

As an occupational hazard among oyster dredgers of the Middle Atlantic coast, "red moss poisoning" must be reckoned with as a cause of contact dermatitis.

136 South Sixteenth Street, Philadelphia.

516 Cooper Street, Camden, N. J.

7. Nelson, T. C.: Report of the Department of Biology of the New Jersey Agricultural Experiment Station, New Brunswick, N. J., for the Year Ending June 30, 1929, p. 104.

A METHOD TO ENHANCE THE VALUE OF BIOPSIES IN DERMATOLOGIC DIAGNOSIS

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Assistant Professor of Pathology, University of Arkansas Medical School
LITTLE ROCK, ARK.

Among clinicians and pathologists alike it is only too well known that biopsies of the skin are on the whole rather unsatisfactory in furthering the diagnosis. The dermatologist, well aware of the solid foundation of his specialty in pathology, is apt to be disappointed by what he may well consider the inadequate performance of individual pathologists who are not quite up to their task. The pathologist again, accustomed to play an eminently helpful role in other clinical fields, like that of diagnosis of tumors will be keenly conscious of the fact that in many instances his efforts will not carry him beyond a mere description of changes in the tissue. These, as he well knows, are not characteristic of any one disease but may fit in with a disconcerting number of cutaneous lesions. It must be emphasized that competent pathologists will find themselves depressingly often in a situation in which they will judge their contribution toward the diagnosis of a dermatologic condition to be insignificant.

It was assumed that well trained clinicians in close cooperation with competent pathologists ought to be able to accomplish a great deal more than they do at present. Therefore, an analysis was made of the clinician-pathologist combination with its mutual responsibilities toward the establishment of a diagnosis. Shortcomings of proper coordination were encountered while appraising the opportunities as well as the limitations of both the clinical and the pathologic lines of investigation. Since properly balanced team work is indispensable in the accomplishment of a task as difficult as diagnosis of cutaneous tissue, suggestions for an increased efficacy of that team are proposed.

A specimen of skin for biopsy is usually submitted to the pathologist together with a more or less elaborate description of the clinical findings. Often this description tends to be brief, the extreme being merely "skin for biopsy," perhaps with an added statement as to the site of removal: "specimen from cheek." However, even if the description is reasonably concise, "Papular, scaly, gyrate lesions from 1 to 3 cm. in diameter, localized mainly on the trunk, of six weeks' duration," the pathologist encounters obstacles while attempting to arrive at a diagnosis.

The all-important point is that the pathologist must approach a dermatologic problem openmindedly of course but with a rather definitely preconceived idea as to the various diagnostic possibilities; the reason for this will be elaborated subsequently. Before studying his slide, the pathologist will therefore have to ask himself: "What are the diagnostic possibilities of this lesion?"

The pathologist, confronted with a mere description of a lesion and attempting to evaluate it in terms of a differential diagnosis, is faced with a task which would often stump an expert dermatologist. He cannot reasonably be expected to be up to this task, and as a rule he is not. He will study the slide with a hazy clinical concept of the case or at times with practically no clinical concept at all, going into the case perfectly cold, as it were. This would be possible and workable only in a field where pathognomonic changes in the tissue are the rule and permit of a definite histologic diagnosis. This is not the case in most phases of tissue work and perhaps least of all in dermatology.

It must also be considered that a pathologist lacking the proper clinical concept of a case is liable to miss some features which might otherwise be diagnostic. If he does not suspect granuloma inguinale to be a diagnostic possibility, he is likely to overlook the presence of Donovan bodies. Many pathognomonic features in dermatologic histopathology are so minute in size, inconspicuous in appearance or demonstrable only by special methods that they will not be found unless looked for deliberately.

If the pathologist fails to work out a differential diagnosis on the basis of the clinical evidence at his disposal, he will then be forced to elaborate it on the basis of the histologic appearance. He will have to ask himself: "Which diseases fit the histologic changes I have encountered?" A reconstruction of clinical entities on the basis of histologic pictures is, however, difficult and often impossible. One needs only to recall the variety of diseases imitating the histologic structure of tuberculosis, not to mention the practically unlimited number of diseases giving rise to "nonspecific" inflammatory pictures, to realize that. One also understands why the pathologist, studying his slide without any preconceived idea, is likely to overlook or treat with insufficient emphasis certain features which otherwise might have been of diagnostic significance. Thereby, he further lessens his chances to recognize a characteristic histologic picture. The pathologic report is then apt to be couched in vague descriptive terms which leave the pathologist as dissatisfied as they are useless to the clinician. Some clinicians like to send patients to the pathologist so that he may see the lesion himself. This will often prove to be a flattering but unavailing gesture. The reason is obvious. Dermatologic cases in which there is need of a biopsy are diagnostic

problems. Except for the rare instance in which a pathologist makes dermatology his special field, he is not equipped by training or experience to do the clinical problem justice. In today's highly specialized medicine there are no masters of all trades.

A combined examination of the patient by both the clinician and the pathologist would be ideal indeed. The clinician would appraise the diagnostic possibilities and could profitably consult with the pathologist as to the most suitable site for removing a specimen for biopsy, the fixing solutions to be used and other technical points. The pathologist, familiar with the appearance of the lesion and also with its diagnostic possibilities, would then approach the study of the section under the most favorable conditions. A combined examination will usually be difficult to achieve, except at clinics where the clinician and pathologist are available together at certain hours. However, if my suggestions are followed, an adequate clinicopathologic collaboration can be obtained just the same.

The salient point is that the clinician is the logical one to furnish the differential diagnosis. Often he alone is in the position to make it. The pathologist must be confronted with the diagnostic possibilities. He can then proceed to confirm them or to rule them out on a histologic basis. The following cases illustrate how a clinical differential diagnosis will greatly augment the usefulness of the pathologist.

CASE 1.—The specimen for biopsy was taken from a crusted lesion with a reddish, irregular, raised surface on the dorsum of the left middle finger. It had grown slowly for the past four months. The patient was a white man aged 42, an undertaker.

Clinical Impression.—The following diseases were considered clinically: (*a*) tuberculosis verrucosa cutis, (*b*) fungous infection, (*c*) lupus erythematosus and (*d*) dermatitis vegetans.

Pathologic Diagnosis.—The pathologic diagnosis was blastomycosis.

In this case the pathologist is in the position to contribute a definite diagnosis, based on the finding of the characteristic organism. The latter was found only after a painstaking search. Were it not for the fact that the clinician stressed the possibility of a mycotic infection, the organism would not have been looked for so assiduously.

CASE 2.—The specimen for biopsy was taken from the right ear of a white man aged 34. The lesions were reddish macules, varying in size from that of a pinhead to 3 cm. in diameter. They were partly covered with adherent scales. They were located on the right ear, encroaching on the scalp and on the dorsum of the left index finger. Clinically, there was no itching. The duration was six months with an insidious onset. The Wassermann reaction was negative.

Differential Diagnosis.—The differential diagnoses considered were: (*a*) lupus erythematosus, (*b*) chronic eczema, (*c*) psoriasis, (*d*) lupus vulgaris and (*e*) seborrheic dermatitis.

Pathologic Report.—The histologic appearance was not that of psoriasis or lupus vulgaris. The atrophic scarring observed in the center of the lesion and the follicular hyperkeratosis pointed to lupus erythematosus as against eczema and seborrheic dermatitis. The pathologic diagnosis was: histologic changes compatible with a diagnosis of lupus erythematosus.

The pathologist could not supply a definite diagnosis but was helpful in ruling out all but one diagnostic possibility considered by the clinician. He also failed to discover evidence of any disease which the clinician might have omitted in his differential diagnosis. The microscopic observations fit in with the diagnosis of lupus erythematosus, but since they were not pathognomonic in this disease, the pathologist confined himself to the statement that the changes were compatible with this diagnosis.

Case 3.—A specimen from a Negro aged 26 was studied. The lesion appeared on the right side of the neck, about 2 inches (5 cm.) below the angle of the jaw. A sinus opened from an indurated and elevated area measuring 4 cm. in diameter. The overlying skin was reddened and fixed. It was somewhat tender. The duration was two months. The Wassermann reaction was negative.

Clinical Impression.—The first choice was tuberculosis, the second choice actinomycosis and the third choice infected branchial cyst.

Pathologic Observations.—There was no evidence to substantiate any of the offered diagnostic possibilities. The changes encountered were merely those of a nonspecific inflammation. A second biopsy might be deemed advisable.

In this case the pathologist was unable to confirm any of the suggested diagnoses. He himself had no definite diagnosis to offer and merely reported a nonspecific inflammation. He suggested another biopsy if the clinical situation warranted it, realizing that another specimen might well reveal fungi, a cyst wall or tuberculous granulation tissue to bear out the clinical impression. A subsequent biopsy revealed an identical picture. The clinical course was in agreement, since the lesion healed uneventfully.

It might have been possible for a specific disease to escape detection. Yet as long as its possible bearing on the case was reckoned with, a relentless search for some definite evidence will be carried on by the clinician and pathologist alike. The pathologist might suggest additional laboratory procedures to supplement the information obtained from the biopsy.

Case 4.—A specimen for biopsy was obtained from the left inguinal nodes, which were considerably enlarged and somewhat tender, of a Negress aged 35. The overlying skin was livid and slightly fixed. No sinuses were found. There was no lesion on the external genitalia at this time, but a history of an ulceration about two months previously was obtained. The Wassermann reaction was negative.

Differential Diagnosis.—The diagnosis was either (*a*) chancroid bubo or (*b*) venereal lymphogranuloma. The incision did not uncover any pus, but the central portions of the lesion were softened and discolored.

Pathologic Diagnosis.—The pathologic diagnosis was lymphosarcoma, and the suggestion was made to rule out lymphatic leukemia with blood studies.

In this case the clinician did not recognize the real nature of the lesion. The pathologist, confronted with a pathognomonic picture, nevertheless made the diagnosis for him.

Should the pathologist want to refresh his memory concerning the histologic features of one or several of the diseases suggested, he can easily consult the literature. This will be of considerable importance, especially when he is dealing with rarer conditions. It is of course impossible if the pathologist lacks a clinical concept of the case.

There can be but little doubt that the method of collaboration between clinician and pathologist herein suggested or some other equally effective plan is already employed where high standards of dermatologic practice prevail. Yet this does not alter the fact that the shortcomings of diagnosis of dermatologic tissue are widely prevalent and that improvements of this diagnostic aid are urgently needed.

SUMMARY

The reasons for the unsatisfactory results obtained with biopsies of skin are analyzed and found to be due to a lack of collaboration between the clinician and the pathologist.

It is suggested that the clinician submit a complete differential diagnosis to the pathologist.

The efficacy of this procedure is demonstrated by a group of cases.

913 Welch Street.

Correspondence

SENSITIZATION TO SULFONAMIDE COMPOUNDS

To the Editor:—The incidence of sensitization to sulfonamide compounds is great enough to warrant limitation of their use to treatment of diseases for which they are indispensable. Since the topical exhibition of these drugs readily leads to sensitization in persons who are susceptible, dermatologists can do much to lessen unnecessary exposure to them.

This is a plea for dermatologists not to cease experimenting with these drugs to seek out their value and place in their field of medicine but to refrain from using them for diseases that are common and for which effective therapy has long been available. I have in mind impetigo and pyoderma. By now, pharmaceutic manufacturers are recommending to members of the medical profession generally these drugs in ointment form for use against the aforementioned diseases. Would it be fair to deprive a patient of sulfonamide compounds for the treatment of pneumonia because previous use of such a drug in a salve for the treatment of impetigo had rendered him sensitive to and intolerant of them?

HERMAN SHARLIT, M.D., New York.

32 East Sixty-Fourth Street.

Obituaries

J. FRANK FRASER, M.D.

1867–1943

Dr. J. Frank Fraser died on Jan. 31, 1943, after an operation for appendicitis. He was born on Jan. 8, 1867, at West River, Nova Scotia, Canada, the son of Colin Fraser, a member of the Municipal Council of Nova Scotia and a Canadian cavalry officer, and Anne MacGilling Fraser.

He graduated from Pictou Academy and Dalhousie University, Halifax, Nova Scotia, Canada, and received his degree of Doctor of Medicine from Bellevue Hospital Medical College, New York, in 1892.

Dr. Fraser returned to Nova Scotia and practiced medicine at Glace Bay and Port Morien for a time. He then came to New York and at first devoted much time to the study of pathology in the laboratory of his brother, the late Dr. Alexander Fraser, formerly professor of pathology at New York University College of Medicine, and held the position of instructor and lecturer in pathology in that institution.

Dr. Fraser later specialized in dermatology, and during his long career he held a number of important positions at various medical colleges and hospitals. At one time he was adjunct visiting physician at Bellevue Hospital, New York. For many years he was chief of clinic of the department of dermatology and syphilology and associate professor of clinical medicine (dermatology) at the Cornell University Medical College, and after its affiliation with the New York Hospital he was appointed, in addition, associate physician (dermatology) at that institution. In 1935 he joined the staff of the Skin and Cancer Unit of the New York Post-Graduate Medical School and Hospital, as associate clinical professor of dermatology and syphilology and chief of clinic. In 1939 he was appointed consulting dermatologist to the New York Post-Graduate Medical School and Hospital. Dr. Fraser was also consulting dermatologist to the Memorial Hospital for the Treatment of Cancer and Allied Diseases, New York, and St. Francis Hospital, Port Jervis, N. Y.

Dr. Fraser was a fellow of the New York Academy of Medicine and at one time chairman of the Section of Dermatology and Syphilology. He was a fellow of the American Medical Association, a member of the American Dermatological Association, the New York and Manhattan dermatologic societies, a fellow of the American Academy of Dermatology and Syphilology and a former member of the Harvey Society and the

Pathological Society. In the last war he served with the rank of Major as President of the United States Army Examining Board for Medical Officers in the city of New York.

Dr. Fraser was possessed of unusual scientific attainments and was a contributor of exceptional merit to dermatologic literature. All during his life he was deeply interested in the histopathology of diseases of the skin. His writings on this subject all revealed careful, thorough work and a sound knowledge of pathology. This combined with his general

J. FRANK FRASER, M.D.
1867-1943

good judgment and well thought-out opinions made him one of the foremost authorities of the day in his chosen field.

His strong yet kindly nature combined with the sound training of an unusually keen mind made him a teacher of great ability. His lectures and clinics were models of clearness and simplicity, and his students were enthusiastic in their praise of his teaching. There was always the most pleasant relation between master and pupil.

His well developed powers of observation, his sound knowledge of pathology and his broad grasp of the general principles of medicine

all combined to make him a clinician of the highest rank. His discussions of cases at clinical meetings were clear and concise, and his opinions were always listened to with close attention.

His strength of personality, his genial disposition and his keen sense of humor made his relationship with his patients and many friends a delightful one, and they mourn the loss of a man of many endearing qualities, considerate, kind and courteous to all.

In the death of Dr. J. Frank Fraser, American dermatology has lost one of its foremost figures; his friends and patients have lost a kindly helpful influence, and those associated with him professionally, a definite stimulus. With a sense of deep appreciation we tender this tribute to the memory of a colleague who held our affection, and we extend our sympathy to his family in their great loss.

Dr. Fraser is survived by a son, Pilot Officer Colin J. Fraser, now serving with the Royal Air Force in India, and by two married daughters.

HANS J. SCHWARTZ, M.D.

Society Transactions

PHILADELPHIA DERMATOLOGICAL SOCIETY

DONALD M. PILLSBURY, M.D., *Chairman*

DOUGLASS A. DECKER, M.D., *Secretary*

Sept. 18, 1942

Purpuric Pigmented Lichenoid Dermatitis of Gougerot and Blum. Presented by DR. DONALD M. PILLSBURY and DR. LESLIE NICHOLAS (by invitation).

J. V. M., a white woman aged 55, has had a painless swelling of the right parotid gland for several years. The skin generally is rather thin and dry. On all aspects of each thigh, leg and ankle and on the ulnar aspect of each elbow and forearm there are numerous tiny, smooth, slightly elevated, sepia-brown papules. These vary in diameter from 0.5 to 2 mm. and tend to become confluent and form plaques. Scattered freely between them are numerous purpuric macules. There are several rather large depigmented areas, and in many places the skin is atrophic and wrinkled. None of the lesions change in color with diascopic pressure.

The eruption appeared eight years ago around each ankle and gradually spread to involve all aspects of both legs and thighs. Three years ago a similar eruption appeared on the ulnar aspect of each forearm and elbow. The lesions have undergone little change. The patient states that after the ingestion of certain foods (e. g., tomatoes) the color of the involved skin becomes more brilliant and then itching develops. The faucial tonsils are enlarged; there is slight axillary and inguinal lymphadenopathy. The blood pressure is 150 systolic and 100 diastolic. Examination of the blood showed 72 per cent hemoglobin, 6,000 leukocytes per cubic millimeter, bleeding time three minutes and clotting time two and one-half minutes. A urinalysis showed a specific gravity of 1.005; there was no sugar or albumin and only an occasional leukocyte and finely granular cast. The report on the biopsy was as follows: The epidermis was atrophic, sometimes being comprised of only three layers of cells. There were striking changes in the neighborhood of the capillaries in the subpapillary region. The number of cells was not great, but polymorphonuclear leukocytes were among them and in one or two places dominated the picture. A few free erythrocytes were intermingled at some places, in which cases the polymorphonuclear leukocytes were eosinophilic and the wall of a nearby capillary severely degenerated. In short, the picture was that of a toxic purpura. There was a scanty amount of pigment, which was finely granular and diffusely distributed interstitially.

DISCUSSION

DR. SIGMUND F. GREENBAUM: Of interest in this case is the smooth atrophic and geographic tongue. The lesions on the extremities are pigmented and purpuric, and I am wondering whether there is any relationship between the progressive pigmentary dermatosis of Schamberg and this disease described by Gougerot and Blum.

DR. CARROLL S. WRIGHT: My own opinion is that nobody knows anything about these diseases. Even Schamberg was never sure about the true nature of progressive pigmentary dermatosis.

DR. SIGMUND S. GREENBAUM: He pointed out, I think, that there is a hypercholesteremia in cases of this kind.

DR. CARROLL S. WRIGHT: Yes, but in some cases there is no hypercholesteremia.

DR. HERBERT J. SMITH: This woman has some lesions on her arms and forearms, which she says come and go. They are lichenoid, I think.

DR. A. STRAUSS: One of those lesions on the arm reminds me of a purpuric lesion following urticaria. It is typical of urticaria; and in the center is the purpuric lesion. I wonder whether the lesions on the leg began in the same way.

Seborrheic Streptodermatitis and Late Syphilis. Presented by DR. MORRIS MARKOWITZ.

D. L., a Negress aged 43, presents an eruption which began about six weeks ago as an acute papulovesicular dermatitis and was made worse after two injections of neoarsphenamine. When first seen, nine days after onset, she presented extensive vesicopustular lesions on the neck, in the axillas and in the inguinal region. Itching was severe and relieved by local applications. The lesions within the borders gradually disappeared and were followed by pigmentation, while leaving persistent denuded margins festooned with vesicopustules. Examination for fungi gave negative results. The Wassermann and Kahn reaction of the blood were strongly positive. A complete blood count was normal. Chemical examination of the blood showed 110 per cent dextrose, 17 per cent urea nitrogen and 1.1 per cent creatinine. The patient has been given resorcinol and boric acid compresses followed by 5 per cent sulfathiazole (2-[paraaminobenzenesulfonamido]-thiazole) ointment.

DISCUSSION

DR. SIGMUND S. GREENBAUM: There are a number of vesicopustules on the right thigh anteriorly, just below Poupart's ligament, and intense itching. I do not think one can altogether rule out a pustular form of dermatitis herpetiformis. It does not appear to me that the syphilis has anything to do with it.

DR. THOMAS BUTTERWORTH, Reading, Pa.: In the history it was stated that this patient has used sulfathiazole, but the results were not given. There is a form of impetigo which occurs in young children which resembles this picture considerably, but I have never seen it in an adult. In a baby I should be willing to accept the diagnosis of impetigo.

DR. BERTRAM SHAFFER: I thought that clinically the eruption was dermatitis herpetiformis, but I do not see how one can definitely rule out the streptococcus as an etiologic agent.

DR. MORRIS MARKOWITZ: I have never seen any grouping, to make a diagnosis of Duhring's disease.

DR. BERNARD L. KAHN: The eruption in this case makes me think of a fungous infection, as most of the lesions occur in the areas where there is an increased quantity of moisture—on the neck and in the groins.

DR. J. M. SCHILDKRAUT, Trenton, N. J.: I had a similar case, in which a woman had three or four attacks. The condition started originally as dermatitis following the application of metaphen (4-nitroanhydro-5-hydroxymercuriorthocresol). She had an operation, and metaphen was used for sterilization of the skin. The dermatitis then started in the pubic region and spread over the lower parts of the abdomen. It involved also the neck, all the flexor regions and the axillas. She recovered from this attack, and some months later another developed, which began in the armpits as vesicopustules. There was no history of local irritation. The vesicles fused, forming large patches with spreading undermined borders and scattered vesicles in adjacent regions. My patient's condition cleared up, however, with application of wet dressing of mild solution of aluminum acetate and administration of sulfathiazole internally. Since then she has had one or

two more attacks and has recovered entirely with the foregoing treatment. I had in mind dermatitis herpetiformis, but the vesicles soon are filled with pus and fuse, forming large impetiginous areas, so that I have considered the condition a recurrent impetiginous dermatitis in a person of low resistance to infection.

A Case for Diagnosis. Presented by DR. DONALD M. PILLSBURY and DR. JOHN W. LENTZ (by invitation).

C. B., a white woman aged 23, presents three discrete lesions on the lower part of the right leg. These originally appeared to be roughly circular plaques of chronic dermatitis with moderate fine scaling. Under local therapy, consisting of application of Castellani's paint, compound ointment of benzoic acid N. F. and crude coal tar, the dermatologic picture appeared as at present. A total of 300 r of roentgen rays was given. Ammoniated mercury and 5 per cent sulfathiazole (2-[paraaminobenzenesulfonamido]-thiazole) ointment were used unsuccessfully to control a secondarily infected area of contact dermatitis involving the right axilla. This process cleared up in several days with the local use of roentgen rays and calamine lotion. The cutaneous lesions on the right leg began four months ago and have persisted, becoming progressively more extensive, with some central clearing. The patient's family and past history are irrelevant except that her sister, who lived with the patient, died of pulmonary tuberculosis. Scrapings examined for fungi were not found to contain any; reports on fungous culture are still pending. A roentgenogram of the chest showed no evidence of tuberculosis. Tuberculin patch tests made Sept. 16, 1942 on homologous areas of the lower parts of both legs showed a strongly positive reaction, greater on the normal leg, with a definite exacerbation of the presenting lesions.

DISCUSSION

DR. JOHN W. LENTZ (by invitation): When Dr. Pillsbury and I saw this patient first, we diagnosed the condition as nummular eczema. The picture has changed under treatment. She had been treated with crude coal tar, and I have wondered whether the therapy had something to do with it. The eruption may be a healing nummular eczema, the clinical appearance of which was changed by crude coal tar.

DR. THOMAS BUTTERWORTH, Reading, Pa.: I think the disease is a fungous infection. I do not see any signs of irritation due to local applications.

DR. CARROLL S. WRIGHT: That was my diagnosis.

NOTE.—Since presentation positive cultures for fungi have been obtained. The lesions have disappeared without further treatment.

Naevus Pilosus, Growing Slowly. Presented by DR. DONALD M. PILLSBURY and DR. ELIZABETH R. CONSTANT.

C. H., a white boy aged 13, presents on the nose a raised lesion about 15 mm. in diameter. It is soft, yellowish and covered by short coarse hairs. There is a central contracting scar, probably the result of previous treatment. The lesion was noticed first three and one-half years ago. Three years ago treatment by the "electric needle" caused no change. Two years ago three roentgen ray treatments were administered without result. The lesion appears to be growing slowly.

DISCUSSION

DR. J. P. GUEQUIERRE: I am not decided as to whether the lesion is a nevus or not. If it is, apparently the previous electrodesiccation destroyed the surface and it is growing underneath, which accounts for the lack of the usual color.

DR. SIGMUND S. GREENBAUM: I think the lesion is a nevus. It should be let alone or removed in toto by a surgeon. It may increase in size as the child grows older.

DR. THOMAS BUTTERWORTH, Reading, Pa.: How do you plan to remove it?

DR. DONALD M. PILLSBURY: Send the boy to a surgeon and have it excised.

DR. THOMAS BUTTERWORTH, Reading, Pa.: In the case of the nose, it is remarkable what good results one can get by removing lesions, even of this size, by electrodesiccation. The results may be as good as those obtained by excision, because a surgeon would take in much more of a margin of uninvolved skin than would be destroyed by electrodesiccation. It might be worth while to electrodesiccate completely and think about the plastic procedure later.

DR. J. P. GUEQUIERRE: I should excise this lesion with the cutting current. A similar-appearing lesion which I treated a year and a half ago turned out to be an amelanotic melanoma.

DR. J. M. SCHILDKRAUT, Trenton, N. J.: In the scarring following electrodesiccation, one often gets a keloid in the center. Therefore, electrodesiccation might not be such a good procedure in this case.

Herxheimer Reaction in Secondary Syphilis Four Days After Massive Therapy (Five-Day Treatment). Presented by DR. SIGMUND S. GREENBAUM and DR. SIMON KATZ.

W. W., a Negro aged 24, presents a disappearing, papular, slightly scaly eruption on the face, chest, back and upper and lower extremities, including the palms and soles. He had gonorrhea five years ago and lymphogranuloma venereum in February 1942. On Aug. 1, 1942 pains in both thighs, headache and fever developed. On August 12 a rash appeared on both forearms, spreading gradually to the entire body. The Wassermann reaction of the blood on August 2 was strongly positive. The five day treatment was instituted from August 22 to August 26, the patient receiving 240 mg. of mapharsen in 2,000 cc. of a 5 per cent solution of dextrose and ascorbic acid, 100 mg. daily. He was discharged on August 28. Two days after discharge the cutaneous eruption, which had almost completely cleared, reappeared, but the lesions were large, papular and twice the size of the original ones.

The patient has palpable right inguinal and posterior cervical nodes. The Wassermann reaction on February 4 had been negative; on August 12 it was strongly positive. The result of a direct van den Bergh test was negative and of an indirect test 0.2 mg. On August 21 the urea nitrogen content of the blood was 15 mg. per hundred cubic centimeters and the sugar content 90 mg., and the carbon dioxide content of the plasma was 58 volumes per cent. On August 28 the sugar content was 77 per hundred cubic centimeters and the urea nitrogen content 13 mg., and the carbon dioxide content was 58 volumes per cent. A complete blood count on August 21 revealed 4,450 erythrocytes and 5,600 leukocytes, with 64 per cent neutrophils, 1 per cent eosinophils, 5 per cent monocytes and 29 per cent lymphocytes. There was 75 per cent (12.5 Gm.) hemoglobin. The examination of the cerebrospinal fluid on August 2 gave negative results. The results of urine were normal, and there was no urobilinogen.

DISCUSSION

DR. SIGMUND S. GREENBAUM: From time to time I have seen Herxheimer reactions in patients treated by the five day method. Those lesions look like papules, but when one feels them they are soft—there is no infiltration.

DR. DONALD M. PILLSBURY: How soon does one ordinarily see a Herxheimer reaction in massive dose therapy?

DR. SIGMUND S. GREENBAUM: In a few days to a week after the start of the therapy. This man started treatment about fifteen days before this complication developed. The probable explanation is that the lesions were in partial development when therapy was commenced.

DR. HERMAN BEERMAN: There is a form of treatment-resistant syphilis called arsenostimulation (Gougerot), in which the lesions actually grow worse under treatment.

DR. SIGMUND S. GREENBAUM: That can happen with bismuth compounds as well as with arsenic compounds.

Pemphigus Vulgaris. Presented by DR. I. ZUGERMAN.

E. A., a white woman aged 43, presents bullous lesions of the body, arms, legs, mouth and vulva. Three months ago she showed lesions resembling lichen planus. The Wassermann reaction of the blood was negative. A blood count showed secondary anemia and eosinophilia. The patient has received 100,000 U. S. P. units of vitamin A, 50 mg. of vitamin B_1, 100 mg. of ascorbic acid (vitamin C), 500 mg. of nicotinic acid and 250,000 U. S. P. units of vitamin D, daily. She has received 60 grains (4 Gm.) of sulfathiazole (2-[paraaminobenzenesulfonamido]-thiazole) a day and acetarsone (0.25 Gm.) twice daily.

DISCUSSION

DR. SIGMUND S. GREENBAUM: The woman says that she feels perfectly well. With the bullae, she has definite petechial lesions on the left leg. The Nikolsky sign can be elicited, and under the piece of epidermis that came away when I elicited this sign there were three or four petechial lesions. I am not convinced that she has pemphigus vulgaris on the general basis of good health with so extensive a bullous eruption, despite a positive Nikolsky sign, the petechial lesions and, of course, the pruritus. I have encountered several cases of a condition which appeared clinically to be dermatitis herpetiformis but which developed into pemphigus vulgaris and also cases of pemphigus vulgaris in which pruritus was fairly severe. The outcome of this case should be reported at a future meeting.

CLEVELAND DERMATOLOGICAL SOCIETY

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JAMES R. DRIVER, M.D., *Reporter*

Sept. 24, 1942

Annular Papular Syphiloderm. Presented by DR. E. B. HEISEL and MAX E. KRAUSE.

M. D., a white woman aged 47, of Polish extraction, presented from the department of dermatology and syphilology, Cleveland City Hospital, complains of hoarseness and an asymptomatic eruption of five months' duration. At the onset the lesions were like "measles," gradually becoming larger and extending to the present distribution.

There is a fairly generalized erythematosquamous eruption involving the face, neck, trunk and upper extremities, while the palms, distal portion of the lower extremities and mucous membranes are spared. The lesions are pink to dull red and consist of small papules, nodules and annular lesions with raised scaly borders and depressed pigmented centers. Some annular lesions have coalesced to form areas with serpiginous borders. The vocal cords are smooth and white and move normally. The epiglottis is normal. Other physical observations are irrelevant.

The hemogram, urine and spinal fluid were normal. Serologic reactions for syphilis were strongly positive. An intracutaneous test with purified protein derivative of old tuberculin in the first dilution gave negative results. Roentgenologic examination of the chest showed no abnormalities.

Microscopic examination of a section taken from a lesion on the abdomen showed only moderate hyperkeratosis in the epidermis. The corium showed a

widespread infiltrate which extended deep into the subcutaneous fat and was for the most part perivascular. This infiltrate consisted chiefly of plasma cells along with epithelioid cells and lymphocytes.

DISCUSSION

DR. R. E. BARNEY: This eruption is most frequently seen in the Negro race. Another feature was the numerous clusters of small papules, the so-called corymbose syphilid.

DR. H. N. COLE: I thought this patient was interesting from the standpoint of the possible relationship to sarcoidosis. The color of these lesions would go well with sarcoid. They are nodular and do not break down. They have been present for some time, so that the cutaneous manifestations might make one think of a sarcoid. Of course, she does not present other manifestations of that disease, and she does present the picture of syphilis.

Lymphogranuloma Venereum with Early Rectal Stricture; Latent Tertiary Syphilis. Presented by DR. E. B. HEISEL and DR. MAX E. KRAUSE.

S. R., a Negress aged 38, presented from the department of dermatology and syphilology, Cleveland City Hospital, complains of frequency of urination, a vaginal discharge and a draining "sore" on the inside of her left thigh of nine months' duration. In the past two months she has lost 24 pounds (11 Kg.) in weight and two similar sores have appeared adjacent to the original one. There are no gastrointestinal disturbances. She has received intermittent irregular treatment for syphilis for the past nine years.

On the inner aspect of the left thigh adjacent to the vulva there is an indurated area 8 by 12 cm. in size in which there are four sinuses draining a sanguinopurulent discharge. Rectal examination reveals an annular fibrous stricture located just above the mucocutaneous junction. There is no perirectal induration. Lymphadenopathy is not remarkable. Other physical observations are irrelevant.

The hemogram showed moderate secondary anemia. The urine and spinal fluid were normal. The reaction to a Kline test of the blood was weakly positive. The reaction to a Frei test was strongly positive and that to an Ito-Reenstierna test negative. Chemical studies of the blood showed a moderate hyperproteinemia and hyperglobulinemia with a reversal of the albumin-globulin ratio. Roentgenologic studies of the rectum showed a rectal stricture with little perirectal inflammation.

Histologic examination of a section taken from the rectal stricture showed ulceration and atrophy of the mucosa. In the base of the ulceration there were an infiltration of polymorphonuclear leukocytes and a slight proliferation of fibroblasts and capillaries. In the mucosa and extending into the submucosa there was a widespread and dense infiltrate composed chiefly of lymphocytes and plasma cells as well as many eosinophils. There were no giant or epithelioid cells.

Therapy consisted of the oral administration of 12 Gm. of sulfaguanidine (sulfanilylguanidine) daily. In addition, fever therapy by the intravenous injection of typhoid vaccine was given.

DISCUSSION

DR. H. N. COLE: I think this woman presents about the earliest example of esthiomene that I have seen in the City Hospital clinic. As nearly as can be made out, the disease has been present for only nine months. I am not exactly sure how long she has had the stricture, but apparently it has not been a long time, for thus far she has had no rectal complaints

A Case for Diagnosis (Lichen Planus? Neurodermatitis?). Presented by DR. E. B. HEISEL and DR. MAX E. KRAUSE.

S. K., a white man aged 74, presented from the department of dermatology and syphilology, Cleveland City Hospital, complains of a pruritic eruption on the

legs and feet of three years' duration. The lesions regress slightly at times but never disappear entirely.

On the legs is a bilateral symmetric erythematosquamous eruption. The anterior surfaces are most severely involved. The lesions consist of sharply delimited round flat-topped deep red papules, 1 to 2 mm. in diameter. There are many excoriations. Many lesions are covered with a dark brown crust and others with a fine scale.

The Wassermann reaction of the blood was negative.

Histologic examination of a section through a papule showed moderate hyperkeratosis, parakeratosis and atrophy of the epidermis. In the subpapillary layer there was some edema with the formation of a clear space. In the upper portion of the corium there was a sharply limited bandlike round cell infiltrate, consisting largely of lymphocytes. Other areas showed moderate acanthosis with a similar infiltrate in the corium.

DISCUSSION

Dr. H. A. Haynes Jr., Akron, Ohio: All I could see on the patient's legs were crusted excoriations. I saw no papules that were suggestive of lichen planus, although there was some mild lichenification surrounding the clusters of excoriated points. I believe he has neurodermatitis circumscripta rather than lichen planus.

Dr. H. J. Parkhurst, Toledo, Ohio: I could not classify this patient's disease as neurodermatitis but felt rather that it might be a senile pruritus localized in that area and aggravated perhaps by contact with dust. I thought the histologic picture was somewhat suggestive of lichen planus but could find no clinical evidence to bear that out.

Dr. H. G. Miskjian: The section could be in no way interpreted as lichen planus. There were elongation of the interpapillary pegs and some edema in the papillary layer of the corium, which suggested what one usually sees in lichenification. I am inclined to think of this condition as a very early stage of lichenification.

Spindle Cell Sarcoma of the Scalp with Metastasis to the Posterior Cervical Nodes. Presented by Dr. Max E. Krause and Dr. E. B. Heisel.

J. D., a white boy aged 11 years, presented from the department of dermatology and syphilology, Cleveland City Hospital, in the past six months has had a recurrence of a growth on his scalp. It started as a small nodule in January 1941 and grew rapidly to the size of a walnut. It was excised at the Cleveland Clinic in May 1941. Several months later the mass reappeared and has grown to its present size. In September 1941 a small mass was removed from the right posterior cervical region. This, too, has recurred.

At the vertex of the skull is a round, shiny, tense, sharply circumscribed tumor of the scalp, 8 cm. in diameter and 5 cm. in height. It is covered by a thin, hyperemic, almost translucent epidermis and is firmly attached to the deep tissues. One area is weeping, this being the site of recent trauma. Around the tumor there is an area of scar tissue about 12 to 15 cm. in diameter. In the right posterior cervical region is a firm oval nontender subcutaneous mass which is attached to the deep tissue and the overlying skin. The skin over it is thin, hyperemic and deep red. The results of physical examination are otherwise normal.

The hemogram and the urine were normal.

Histologic examination of a section of the tumor showed a margin of comparatively normal skin. In the lower part of the corium and in the subcutaneous fat there was an extensive invasion of large spindle-shaped cells. The cytoplasm was pink and fibrillar. In many instances the cytoplasm was long and ribbon-like. Clearcut cross striations were not seen after a moderately prolonged search. The nuclei were large, oval and rather pale staining with stippled chromatin markings. There were numerous mitotic figures. There were areas of degeneration in which

nuclei were scant and only a little fibrillar material was left in the cells. Blood vessels were not numerous. In places there were vascular spaces lined only by tumor cells.

DISCUSSION

DR. J. R. DRIVER: I believe that if one had not seen the histologic section one would think of a melanoma, possibly originating from a melanotic lesion in the scalp, perhaps irritated by a comb. The patient gives a history of trauma several years ago, when he was about 6 years old, and whether that has been a factor in the development of the lesion or not is questionable, but I think it could have been. Now the question comes up as to what kind of therapy should be used here. Surgical excision was performed at one time and the lesion recurred. I should now be inclined to favor the use of interstitial irradiation with low intensity radium platinum needles. This could be supplemented with filtered roentgen therapy given by the Coutard technic. This combination makes it possible to take advantage of the cross fire technic. The prognosis is bad, but not necessarily hopeless.

DR. E. B. HEISEL: We saw this patient first in the accident room of the hospital, because he had fallen, injuring the tumor and causing it to bleed rather profusely. We plan to make roentgenograms of the skull before therapy is instituted.

A Case for Diagnosis (Epithelioma? Sarcoma?). Presented by DR. G. M. STROUD.

L. J., a 63 year old stationary engineer, presented from the department of dermatology and syphilology, University Hospitals, complains of a crusted swelling of the nose of nine months' duration. He has had hypertension, tinnitus and occasionally epistaxis for several years. For a number of years he has had "hay fever" but no bronchial asthma or eczema. About nine months ago he noted several flesh-colored papules on the right side of the nose, which gradually enlarged. Several months later in another city he had four roentgen ray treatments without improvement. At about this time he treated the area for about a week with applications of a mixture of eggs, vinegar and turpentine, resulting in the formation of black crusts. The growth become more extensive and was associated with a clear nasal discharge. About three weeks ago he noted a lump on the left side of the jaw.

There is a fairly symmetric dull red enlargement of the nose which is covered with a black crust. Induration extends from this tumor to the inner canthus of the left eye. Also, a cordlike infiltration extends across the cheek to a metastatic lymph node involvement at the angle of the left jaw. Nasopharyngoscopy revealed only crusting of the nasal passages.

The hemogram and urine were normal. The Kline reaction was negative.

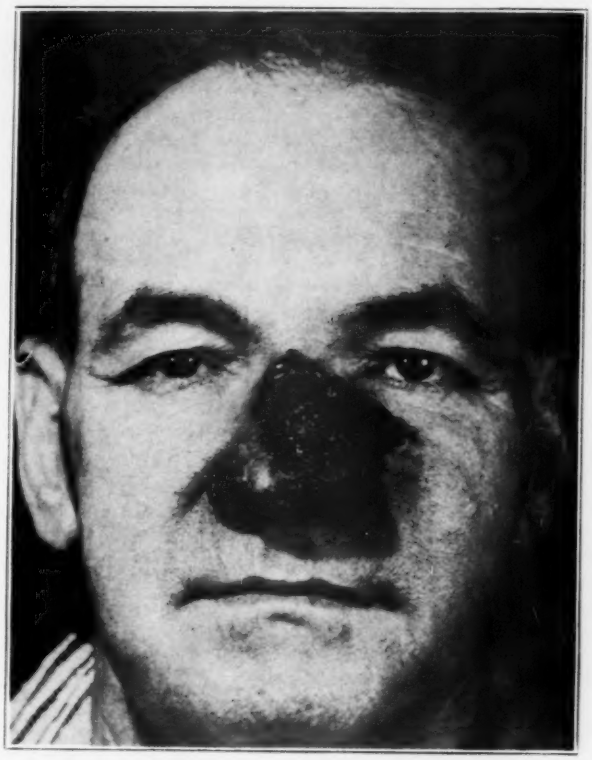
The biopsy specimen consisted almost entirely of tumor. Along one edge was a thin layer of stratified squamous epithelium that showed slight keratinization. In the corium there were small hair follicles and epithelium-lined spaces containing keratin. The tumor was richly cellular and showed considerable pleomorphism. The tumor cells were for the most part elongated and spindle shaped. They had abundant slight acidophilic cytoplasm and relatively large nuclei. Some of the nuclei were hyperchromatic and contained large nucleoli. In addition, there were lymphocytes and eosinophils scattered throughout. In the section stained with Van Gieson stain there were only few small bits of connective tissue among the tumor cells.

In the opinion of the pathologists at the Institute of Pathology of Western Reserve University School of Medicine a diagnosis of leiomyosarcoma was indicated by the histologic evidence.

DISCUSSION

DR. H. N. COLE: It is unusual to have the opportunity of observing 1 case of sarcoma at any dermatologic meeting, but when 2 of them are presented at one

meeting it is most extraordinary. I do not think that I have encountered more than 1 or 2 sarcomas of the skin in my entire practice, and this case is most unusual. The lesion is not of the cherry red color that one would expect to see in a sarcoma and that one reads of in the literature and that has been seen in patients at meetings. Zeisler reported a case of such a lesion some years ago (Zeisler, E. P.: Sarcoma of Skin, *J. A. M. A.* **69**:111 [July 14] 1917). There was a difference of opinion concerning the histopathologic structure of the tumor in the present case. I thought at first that it was an undifferentiated epithelioma, but Dr. Driver felt the picture was that of a reticulum cell sarcoma. Dr. Harry Goldblatt agreed with Dr. Driver.



A case for diagnosis (epithelioma? sarcoma?).

Dr. George M. Stroud: Dr. Karsner and Dr. Goldblatt, pathologists at the University Hospitals, thought that the tumor was definitely a sarcoma. By exclusion they believed it might possibly be a leiomyosarcoma because of the lack of palisading as seen in a neurogenic sarcoma and the extreme paucity of connective tissue in the Van Gieson stained section, which would rule out a fibrosarcoma. There were no smooth muscle cells however.

Note.—The histologic diagnosis of the excised metastatic lymph node was epithelioma. The lesion of the nose was treated with divided doses of roentgen rays. A total of 2,500 r was administered to each side. The metastatic involvement was treated by interstitial irradiation with low intensity radium needles.

Congenital Ectodermal Dysplasia. Presented by Dr. E. B. Heisel and Dr. Max E. Krause.

H. K., a white man aged 27, presented from the department of dermatology and syphilology, Cleveland City Hospital, complains of being unable to stand the summer heat. He does not remember ever sweating and has always had a sparsity of hair on his body. There is no family history of any similar disturbance. He is married and has one normal son.

The skin on the entire body is dry, soft and of a fine texture. That of the palms is hyperkeratotic and dry. On the face, especially around the eyes and mouth and on the sides of the neck, are many pinhead-sized to split pea–sized yellowish brown lesions. The eyes are normal. The nose is small, saddle shaped, covered with atrophic skin and lined by atrophic mucous membrane. The lips are thick and dry. The only erupted teeth are two lateral incisors and two canines in the upper jaw and two canines in the lower jaw. The hair on the scalp, chest and in the axillas is lanugo-like. That on the face is normal. There is no pubic hair. The nails are normal.

The hemogram and urine were normal. The Wassermann reaction of the blood was negative on nine occasions, while the reaction to a Kline diagnostic test varied from negative to strongly positive. Roentgenologic examination of the chest showed nothing abnormal and of the tibias no evidence of periostitis.

Histologic examination of a section of skin taken from the left axilla showed mild hyperkeratosis, keratotic plugs in dilated follicular orifices and intracellular edema of the epidermis. The hair follicles and sebaceous glands were normal. There was an absence of sweat glands. A specimen taken from the skin of the neck showed moderate hyperkeratosis, a small area of parakeratosis and mild intracellular edema of the epidermis. There were a few normal hair follicles and one which appeared much smaller than normal. The follicular orifices were dilated and filled with keratotic plugs. Some sebaceous glands were normal while others were disorganized. No sweat glands were found. There were several epidermoid cysts filled with amorphous material which communicated with the overlying cutaneous surface.

DISCUSSION

Dr. J. E. Fisher: I agree with the diagnosis as presented. However, in view of the fact that there appears to be serologic evidence of syphilis in addition to a deformity of the nose suggestive of congenital syphilis, one would have to consider syphilis as a possible etiologic factor.

Dr. H. N. Cole: It would seem to me that all the symptoms that this patient presents are due to congenital ectodermal dysplasia. The saddle nose is a part of that disease, as is also the absence of teeth. The paucity of hair on the body and the almost complete absence of hair on the scalp also goes with it. It was interesting to speak to the man and find that he, like many others with this condition, is uncomfortable in the summertime because he does not perspire.

Dr. H. A. Haynes Jr., Akron, Ohio: Does the patient give any history of petit mal or epileptiform attacks? I was thinking of the syndrome of epiloia, because the lesions on his cheeks seem to be typical adenoma sebaceum of the Pringle type.

Dr. E. B. Heisel: There is no history of epilepsy that I know of.

Dr. R. E. Barney: There were some other lesions that were interesting. They were milia-like lesions occurring especially around the temples and also on the neck and face. They seemed to assume a linear character, especially on the neck. I wonder if a specimen for biopsy has been taken from those areas and what it showed. I saw one section that did not show the changes one would expect from a clinical examination of that lesion.

Dr. E. B. Heisel: One specimen for biopsy was taken from the axilla and another from the side of the neck. The one from the neck included one of these milia-like lesions. It was shown to be an epidermoid cyst.

DR. M. J. GIBANS, Akron, Ohio: I observed a case (MacKee, G. M., and Andrews, G.: Congenital Ectodermal Defect, ARCH. DERMAT. & SYPH. **10**:673-701 [Dec.] 1924), and this one is almost the exact duplicate in every respect. MacKee called the condition the major type of congenital ectodermal defect.

Dermatitis Exfoliativa. Presented by DR. MAX E. KRAUSE and DR. E. B. HEISEL.

T. M., a white man aged 58, presented from the department of dermatology and syphilology, Cleveland City Hospital, complains of a generalized cutaneous eruption of two and one-half years' duration. The eruption started on the head and spread downward until within four to five months it became generalized. He has lost 40 pounds (18 Kg.) in weight. There is no drug, contact or allergic history. Seven years ago he was treated with electrodesiccation and roentgenotherapy for a papillary carcinoma of the bladder. There has been no recurrence.

There is a generalized erythematous desquamating dermatitis involving the entire body. The epidermis is thickened and infiltrated. In the dry areas it is covered with grayish yellow plaquelike scales, while in the moist areas it is macerated. The axillary and inguinal nodes are palpable. The prostate is small and firm.

The hemogram showed 4,180,000 erythrocytes and 15,000 leukocytes per cubic millimeter. The differential count was 44 per cent polymorphonuclear neutrophils, 40 per cent lymphocytes, 6 per cent monocytes, 7 per cent eosinophils and 3 per cent basophils. Roentgenograms of the chest revealed no evidence of parenchymatous infiltration of the lungs or any increase in the mediastinal content. Reactions to serologic tests for syphilis were negative.

Histologic examination of an inguinal node revealed normal architecture. There was a focal infiltration of plasma cells and an occasional phagocytic cell containing brown pigment which appeared to be hemosiderin. The appearance was not that of a lymphoma.

Therapy over a two and one-half month period has consisted of symptomatic care, including soap and water baths, potassium permanganate baths and application of emollients. There has been a definite improvement in the texture of the skin, with areas of normal skin appearing particularly over the arms.

DISCUSSION

DR. H. J. PARKHURST, Toledo, Ohio: This eruption does not correspond with any type of dermatitis exfoliativa that I am familiar with. There are distinct normal islands, particularly about the sides of the hands. The lesions on the hands are sharply marginated, the size of a small coin, with a collaret about each one, and, although there was no involvement of the mouth that I could find, I thought of the possibility of pemphigus foliaceus.

DR. E. C. STERN: I saw this man two and one-half years ago. The lesions started on his back and chest in circinate red scaly patches and developed into typical pemphigus. Nikolsky's sign was positive. I followed this patient for about eight months, and every now and then during this period he has also shown lesions in his mouth. I now think that he presents the picture of pemphigus foliaceus.

DR. R. E. BARNEY: One should consider the possibility of this being a lymphoblastoma, regardless of the fact that the lymph node excised showed no evidence of one of the lymphoblastomas at the time it was removed. The differential blood count showed that there is a slight lymphocytosis, and therefore one should keep that possibility in mind. It might be well to perform a biopsy of the skin in order to see if there are any suggestive changes there.

DR. E. B. HEISEL: When this man was admitted he was covered with thick greasy scales. Since he has been observed by our service in the past three months he has not had any type of bullous lesions. In answer to Dr. Barney's question, a specimen of skin was removed for biopsy, and it was lost by the pathology department. It took from six to eight weeks to get the ulcer cleared up that occurred at the site of removal of the biopsy specimen, and we rather hesitated to make any more incisions in his skin.

DR. L. L. PRAVER, Columbus, Ohio: The crusts on the back of the hands suggested that vesicles may have been present.

DR. H. N. COLE: I am interested in these remarks about pemphigus foliaceus. No bullae have been seen on this man at any time, and it certainly would be unusual to see pemphigus foliaceus that would last for three years. Pemphigus foliaceus is usually considered a rather malignant disease. I do not think this man has had lesions in the mouth since he has been under observation.

Secondary Syphilis; Bilateral Optic Neuritis and Retinitis. Presented by DR. MAX E. KRAUSE and DR. E. B. HEISEL.

L. S., a white woman aged 25, presented from the department of dermatology and syphilology, Cleveland City Hospital, complains of an eruption on the vulva and "spots" before the eyes of five months' duration.

Examination of the eyes reveals normal eyelids and pupils. The right fundus reveals a papillitis producing 2 diopters of papilledema. There are three small areas of healing retinitis 1 disk diameter inferior to the papilla. The left fundus reveals a papillitis producing 4 diopters of papilledema. There is a small area of active retinitis 1 disk diameter medial to the papilla. The maculas and vessels in both fundi are normal. The retinal imperfections produce some contortion of image. There is a slight constriction of both visual fields but no anopsia or scotomas. The patient presents typical condylomata lata of the vulva.

Dark field examination of serum from the vulvar lesion revealed Spirochaeta pallida. The Kline reaction was strongly positive. The spinal fluid was normal. The hemogram and urine were normal. Roentgenograms of the skull and sella turcica were normal.

Antisyphilitic therapy has consisted of twelve intravenous injections of mapharsen of 60 mg. each and four intramuscular injections of bismuth subsalicylate of 200 mg. each over a period of four weeks. Seven paroxysms of fever were produced by the intravenous injection of typhoid vaccine. One per cent atropine sulfate was used as a mydriatic. As a result of this therapy the vulvar lesions healed rapidly, but there has been only slight improvement in the optic neuritis and retinitis.

DISCUSSION

DR. G. W. BINKLEY: Optic neuritis and retinitis are, in my experience, infrequent manifestations of early syphilis. I do not recall having encountered a similar case in the past ten years. An interesting feature of the ocular involvement is its poor response to chemotherapy. Usually some form of fever therapy is needed as adjunct treatment. In this case the slow response of the optic neuritis can be contrasted with the rapid healing of the cutaneous lesions. The optic neuritis and retinitis are still present; the condylomas are gone.

DR. J. R. DRIVER: What is the opinion of the hospital ophthalmologic consultant?

DR. E. B. HEISEL: The patient was seen by three ophthalmologists. They believe that these changes are due to syphilis.

DR. R. E. BARNEY: Has this patient been given potassium iodide? I think it might be well to give rather large doses of this drug. Since the ocular condition has not responded to the therapy received, I think malarial therapy should be considered.

DR. H. N. COLE: One certainly does not encounter many cases of early syphilis with the changes that are presented here. I should expect that one would get response from the typhoid-paratyphoid injections, but certainly if she does not respond to the fever therapy that she has had already along with the arsenical and bismuth therapy, malaria will be used. I think this case teaches that in all cases of early syphilis there should be careful examination of the eyegrounds.

DR. E. B. HEISEL: There has been moderate improvement in this woman's eyes. The disease has been entirely resistant to treatment, but the response has not been what one would expect. There has been improvement in vision and in the inflammatory process of the fundi.

NEW YORK ACADEMY OF MEDICINE, SECTION OF DERMATOLOGY AND SYPHILIS

FRANK C. COMBES, M.D., *Chairman*

PAUL GROSS, M.D., *Secretary Pro Tem*

Oct. 6, 1942

Lupus Erythematosus Disseminatus Subacutus. Presented by DR. E. WILLIAM ABRAMOWITZ.

V. Z., a woman aged 28, is presented from the Skin and Cancer Unit of the New York Post-Graduate Medical School and Hospital, with an eruption on the face, back, chest and arms. The patient states that in September 1941 she had a rough scaly spot on the bridge of the nose which got worse when she was exposed to the sun. Four months ago, following exposure to the sun, the eruption appeared on the face, chest, back and arms. She had never experienced this reaction previously.

The patient presents an erythematous, slightly scaly, diffuse eruption which is associated with occasional itching.

The Wassermann and Kahn reactions of the blood were negative. The urine was normal. A blood count revealed 3,910,000 erythrocytes and 5,650 leukocytes, with a differential count of 50 per cent neutrophils, 34 per cent lymphocytes, 11 per cent band forms, 4 per cent monocytes and 1 per cent eosinophils. There was 81 per cent hemoglobin.

The patient is receiving weekly injections of a bismuth compound.

DISCUSSION

DR. DAVID BLOOM: This case teaches that even a tiny lesion of lupus erythematosus on the face may develop into disseminated lupus erythematosus after excessive exposure to the sun.

DR. ADOLPH ROSTENBERG: I have under my care a patient like this one. A man about 35 years of age had a small lesion on the neck which looked typical of lupus erythematosus. He got a severe sunburn at the seashore this summer, soon after which a disseminated form of the eruption developed on the scalp. It would have been difficult to diagnose the original lesion if it had not been for the history of a sunburn.

DR. E. WILLIAM ABRAMOWITZ: The acute type of eruption has attracted considerable interest from the internists. As a matter of fact, in some institutions patients with this eruption are no longer admitted to the dermatologic service on account of the possible connection between this eruption and the Libman-Sachs syndrome. The question is whether acute disseminated lupus erythematosus is the same disease as the chronic discoid type. Many dermatologists have not had sufficient opportunity to observe patients with the chronic discoid type of lupus erythematosus over a long period in order to see what happens to them ultimately. It is not known whether they are entirely cured or have relapses and finally die with a typical picture of acute disseminated lupus erythematosus. I think that every patient with lupus erythematosus should be presented with a report of the roentgen observations of his chest and the results of the physical examination, such as any possible renal changes and enlargement of the spleen.

Pemphigus Erythematosus (Senear-Usher). Presented by DR. DAVID BLOOM.

C. L., a woman aged 52, is presented from the Skin and Cancer Unit of the New York Post-Graduate Medical School and Hospital with an eruption in the mouth and on the face, trunk and extremities, associated with itching, which has

recurred for the past fifteen years. In spite of treatment in the clinic since August 1940 with sodium arsenate and injections of liver extract, the patient in the last six months has presented a severe bullous eruption involving the mouth, face, trunk and extremities. Two weeks ago treatment with autohemotherapy was begun, after which she improved considerably. She now presents mostly crusted lesions, the result of broken bullae.

The result of a patch test with 20 per cent potassium iodide was negative. Wassermann and Kahn reactions of the blood were negative. The urine was normal. The last blood count revealed 4,130,000 erythrocytes and 6,350 leukocytes, with 67 per cent neutrophils, 20 per cent lymphocytes, 4 per cent eosinophils, 3 per cent monocytes and 6 per cent band forms. There was 85 per cent hemoglobin.

Histologic examination resulted in a diagnosis of toxic bullous dermatitis.

DISCUSSION

DR. E. WILLIAM ABRAMOWITZ: I happened to see this patient for the first time at the clinic and at first thought of dermatitis herpetiformis. The eruption was itchy. Biopsy was not of great help. On close inspection tonight I am inclined to favor the diagnosis of pemphigus vulgaris. The patient shows considerable improvement. Patients with pemphigus may have the disease for a long time, and that fact alone should not exclude the diagnosis if other symptoms point to it.

DR. DAVID BLOOM: This patient is presented today because of the considerable improvement which has taken place following four injections of her own blood.

Necrobiosis Lipoidica Diabeticorum. Presented by DR. EUGENE TRAUGOTT BERNSTEIN.

M. M., a woman aged 56, is presented from Beth David Hospital with an eruption on both legs of two and a half months' duration. The patient has had diabetes for four or five years. The diabetes is controlled at present.

The patient presents hard, lentil-sized, peripherally growing, raised papules with a surrounding violet-red zone. The lesions are partly ulcerated and necrotic. These nodules have passed through several phases. They began as fawn-colored nodules, increased in size and gradually became necrotic in the center. In the entire region of involvement the skin is a sulfur-yellowish color.

Chemical examination of the blood revealed total cholesterol 240 mg., blood sugar 125 mg., urea nitrogen 16 mg., uric acid 3.8 mg. and creatinine 1.5 mg. per hundred cubic centimeters. The urine was free of sugar. The basal metabolic rate was —18 per cent; she received thyroid and lost about 20 pounds (9 Kg.). The eruption has improved considerably.

The histologic diagnosis by Dr. David Satenstein was necrobiosis lipoidica diabeticorum.

DISCUSSION

DR. CHARLES S. MILLER: At present I should not make this diagnosis clinically. The differential diagnosis histologically must be made between necrobiosis lipoidica diabeticorum and granuloma annulare. As Dr. Bernstein pointed out, there is a superficial vascular reaction in necrobiosis lipoidica diabeticorum with lipid deposits interspersed between the connective tissue bundles. In granuloma annulare there is a granular degeneration of the collagen bundles with a cellular reaction about them.

DR. EUGENE TRAUGOTT BERNSTEIN: At present, morphologically, the picture fits in more with that of papulonecrotic tuberculid. The outstanding features revealed by the biopsy were the necrosis of the collagen and a large number of extracellular fat droplets. Some foam cells were also present, probably as a result of the taking up of locally deposited lipid. It would be difficult now to make a diagnosis from the clinical picture, but in 1932 Urbach described the disease as multiple tissue damage of the skin with extracellular lipid deposits.

Urbach stated that there is a resemblance to erythema induratum and to Darier-Roussy sarcoid. In a case of necrobiosis lipoidica diabeticorum described by W. Noel Goldsmith, which was clinically and histologically unmistakable, the patient had no diabetes but did have a tuberculous background. He therefore concluded that scleroderma-like erythema induratum and necrobiosis lipoidica have practically the same clinical pictures in different phases.

Xanthoma Tuberosum Multiplex. Presented by DR. EUGENE F. TRAUB.

C. L., a woman aged 66, is presented from the Skin and Cancer Unit of the New York Post-Graduate Medical School and Hospital, with an eruption on the extensor surfaces of the forearms, elbows, backs of the hands, knees, backs of the thighs and buttocks of two years' duration. The patient had an operation on the gallbladder twenty years ago.

On the extensor surfaces of the forearms are numerous flattened tumors, violaceous red with a faint yellowish tinge and of various sizes up to a diameter of 1 cm. Their surface is smooth, and they are not raised more than 1 mm. above the surface of the skin. On the elbows are larger tumors, with a diameter of 2 cm. and of a much more irregular shape. On the backs of the hands the lesions are flat and resemble granuloma annulare in some respects. There are many small papular lesions on the knees, backs of the thighs and buttocks. Just below the knees is a group of lesions that suggest lichen planus.

The urine was normal. The blood cholesterol was 310 mg. per hundred cubic centimeters and the blood dextrose 90 mg.

Histologic examination of a lesion from the knee showed the corium to be filled with nodules consisting of round and pale-staining cells and occasional multinucleated cells. Many of the blood vessels had thick walls. In the nodules some of the cells showed a yellowish stain. Stains for fat gave positive results.

Biopsy of a specimen from the hand revealed an acanthotic epidermis. In the upper part of the corium were islands and strands of large pale-staining cells. The outlines of the collagen fibers were blurred. At one end of the section was found the peculiar strandlike degeneration of the collagen fibers that is seen in the center of granuloma annulare. Stains for fat gave positive results.

A section from the elbow showed strands and nodules of large pale-staining cells and numerous round cells, lymphocytes, polymorphonuclear leukocytes and fragmented cells.

A Case for Diagnosis (Symmetric Tertiary Eruption of Syphilis). Presented by DR. MAURICE J. COSTELLO.

J. M., a man aged 60, from the dermatologic wards of Bellevue Hospital, presents a bilateral symmetric ulcerative eruption on the arms and forearms of five years' duration and an inflammatory eruption of discrete large papulopustules on the face, chest and back, which has been present for two weeks. The Wassermann reaction of the blood at the onset of the former eruption is said to have been positive. He received many injections in the arm and hip from his private physician over a period of two years without apparent benefit; the destructive, ulcerative eruption continued to invade contiguous areas. He stated that a "lump" developed in the right parietal region about the time the eruption first appeared on the upper extremities. This lesion of the bone was still present on the date of his admission to Bellevue Hospital, on Sept. 10, 1942, and proved to be a syphilitic osteitis on roentgenographic examination of the bones of the skull. It appeared to be undergoing involution.

The patient presents two types of eruption: One, completely encircling the upper extremities, extending from the insertion of the deltoid muscle to the wrist, is a deeply destructive, ulcerative, sharply circumscribed process with a severe degree of secondary infection and crusting. The other eruption followed the administration of 10 drops of the saturated solution of potassium iodide three

times a day over a period of two weeks. Local therapy which improved the eruption consisted of the application of sulfathiazole powder, zinc peroxide paste and alibour water (aqueous solution of zinc and copper sulfates).

DISCUSSION

DR. HERMAN GOODMAN: In spite of the bilateral symmetry of the lesions, this man has syphilis. He has had a gumma of the bones of the head, verified by roentgen examination. Small doses of iodides, given at the suggestion of Dr. Combes, have resulted in eradication of the osseous gumma. The doses given were very small, yet the man showed a reaction to the iodide. Local therapy applied to the lesions on both arms may have resulted in some improvement of the ulceration. All told, the patient received 50 grains (3.24 Gm.) of iodide in two weeks. The improvement, if due to the ingestion of the iodide, must have resulted from some catalytic action of the drug. Explanation of the mode of action through saturation of nonfatty acids of the gummatous process has been offered, however. It may explain part of the result of iodide therapy.

DR. LEO SPIEGEL: This man has lesions on both sides of the tongue, white patches which do not seem acutely inflammatory. I should like an expression from the members as to whether he has leukoplakia or lingus geographica. Further observation is necessary before a diagnosis can be made.

DR. CHARLES WOLF: I thought the grayish patches on the tongue were leukoplakia. In addition, there is an acute glossitis on an underlying interstitial glossitis. The latter may be a manifestation of ariboflavinosis, as the patient is the type of person who probably does not eat the proper kind of food. If other symptoms improve on antisyphilitic treatment while the condition of the tongue does not, then vitamins may produce an improvement. The acute lesions of the tongue may then be considered a manifestation of avitaminosis.

DR. MAURICE J. COSTELLO: I think this case is unusual from the clinical viewpoint because the eruption is bilateral and symmetric, which is a rare distribution in tertiary eruptions of syphilis. It is also unusual because these lesions have been resistant to prolonged therapy with the arsenicals and bismuth; peculiarly, the only therapy which has helped the condition has been nonsyphilitic treatment, such as applications of sulfathiazole powder, alibour water and zinc peroxide paste. The diagnosis has not been confirmed because the Wassermann reaction of the blood has not yet been determined. Examination of the spinal fluid shows no abnormalities. I agree with those who consider the patches on the tongue leukoplakia. Some of the patches are keratotic, and they have been present for a long time.

A Case for Diagnosis (Melanoma?). Presented by DR. FRANK VERO.

J. D., a boy aged 15, is presented from the Vanderbilt Clinic, where he was previously treated for plantar wart and dermatophytosis of the feet. About four years ago the mother noticed a dark line on the toe nail, extending from the proximal end of the nail bed to the free edge. During the past three months practically the entire nail has become discolored and a small nodule appeared in the posterior nail fold, from which some pus escaped. At that time he had an enlarged gland in the right popliteal region.

The nail plate of the affected toe appears brownish black with a deep fissure in the center. In the posterior nail fold a small, pea-sized, hard nodule is palpable, with deep pigmentation at the periphery and slight ulceration of the surface.

Microscopic examination and culture for fungi gave negative results. Roentgen examination of the toe showed no abnormality of the bones.

DISCUSSION

DR. EUGENE TRAUGOTT BERNSTEIN: I believe the patient has a melanoma. It is difficult to diagnose because he changed the appearance of the nail by scraping, making it look today like onychomycosis. There is a brownish black firm nodule.

DR. E. WILLIAM ABRAMOWITZ: This lesion is what is called a melanotic whitlow. Should one go ahead and remove the toe or take more radical action? A roentgenogram of the bone and particularly of the chest should be made, because frequently before anything startling is noticed at the primary area there is evidence of metastasis elsewhere.

DR. CHARLES WOLF: At present at the hospital I have a patient 76 years old who had a melanocarcinoma of the foot which was treated for two or three years in an expectant manner. Various diagnoses were made. Recently he came under my observation, and the diagnosis of melanocarcinoma was made by histologic study. The question of treatment came up. The radiotherapist decided that amputation should be performed, but the family opposed this and after consultation it was decided to give him the benefit of roentgen therapy. No metastases so far are discernible.

DR. FRANK VERO: I also believe that this boy has a melanoma which was preceded by a pigmented nevus under the nail. In many cases reported in the literature melanotic whitlow began with a pigmented nevus under the nail. Both the boy and the mother are definite that the present condition began with a narrow longitudinal pigmented band extending over the entire length of the nail and that only during the last three months did the entire nail become involved.

Kaposi's Sarcoma. Presented by DR. JOSEPH L. MORSE.

Y. C., an Italian man aged 78, is presented from the Hospital for Joint Diseases. Eight years ago small dark red spots appeared on the toes and feet, and these gradually spread over the legs. Several months ago a few new lesions appeared on the backs of the hands; one of these has enlarged rapidly and has bled on the slightest trauma.

The patient presents characteristic bluish red nodules and plaques on the backs of the feet and toes, legs and thighs and hands and forearms. One nodule on the back of the right hand is crusted.

Biopsy of a specimen taken from the crusted nodule on the right hand showed the epithelium to be ulcerated in places. Beneath the epithelium the cutis was occupied by a number of nodules which extended up to the epithelium. The nodules were composed of decussating bundles of spindle-shaped connective tissue cells. Many mitoses were present. There were many dilated capillaries. The histologic diagnosis was Kaposi's sarcoma.

DISCUSSION

DR. CHARLES S. MILLER: I think there is no question as to the diagnosis. I was interested in the mass on the back of the hand, which I believe has reached the sarcomatous stage. The patient should be thoroughly examined for evidence of internal involvement.

DR. FRANK C. COMBES: Dr. Douglas Symmers is interested in the relationship between Kaposi's sarcoma and vitamin K. Dr. Morse might get in touch with Dr. Symmers.

DR. JOSEPH L. MORSE: This case is interesting from both the clinical and the pathologic standpoint. Here is an instance in which Kaposi's sarcoma remained stationary and inactive for years and then suddenly new lesions appeared and showed great activity. Symmers, in a comprehensive paper (Kaposi's Disease, *Arch. Path.* **32**:764-786 [Nov.] 1941) stated that the fibroblast is the unit of growth and determines the behavior of the lesions. It may produce collagenous fibers which aid in healing and may maintain a low capacity for growth over a long period. However, it may suddenly assume active malignant properties and metastasize. This is brought out in the case presented. Histologically, there is little collagen being formed, and that accounts for the activity and growth of the new lesion. In his article, Symmers suggests the use of vitamin K. I shall try it in this case and report its effect.

Raynaud's Disease with Sclerodermatous Changes. Presented by Dr. Max Scheer.

L. Z., a man aged 45, registered at the Skin and Cancer Unit of the New York Post-Graduate Medical School and Hospital on Sept. 29, 1942, complaining of severe pain and ulcerations of the fingers. The family and personal histories were irrelevant. He has been working at a knitting machine for eighteen years. He does not smoke. He has been feeling well except for indigestion when he eats meat and for nocturia.

Eight years ago he began to feel numbness in all his fingers when he washed his hands with cold water and also during the cold weather. They would turn white and then blue and would resume their natural color on getting warm. This condition gradually grew worse. Five years ago the tip of the right index finger began to ulcerate and "gangrene" set in. He was treated with a proprietary ointment, diathermy and intravenous injection of saline solution for two weeks, when the ulcer healed. Two years ago the left middle finger began to ulcerate. He was treated in a similar manner, the ulcer healing in six weeks. Five months ago the right middle finger ulcerated, but the physician was unsuccessful in healing it with the same method.

The patient has no numbness unless exposed to cold and has pain only when ulcerations occur. The pain stops when the ulcers heal. The pain now is limited to the third, fourth and fifth fingers of the right hand. It is continuous, severe, sharp and cramplike and becomes worse at night. The ulcerations usually extend to about the middle of the flexor surfaces of the distal phalanges, never on the dorsal surfaces.

The soles and the toes have reacted to cold with similar changes of color but have never ulcerated.

Examination shows the terminal and distal phalanges of all the fingers except the thumbs to be curved, bluish, thickened and of boardlike hardness. The right hand is somewhat edematous, and the tips of all the four fingers show ulcerations and crusting. They are painful and tender. He is unable to flex them completely. There are numerous discrete pea-sized ivory-white hard spots, level with the surface of the skin, on the trunk and extremities, most numerous on the upper part of the back. The patient states that a little papule forms first, followed by a scab, which falls off, leaving a white spot. On the scalp are seen several painless pea-sized purplish red macules which on palpation show a slight depression. The feet are bluish and cold. The dorsalis pedis arteries are small but distinctly palpable.

Neurologic examination by Dr. Eisendorfer did not reveal pathologic organic changes in the central nervous system.

DISCUSSION

Dr. Eugene Traugott Bernstein: In my estimation, Raynaud's syndrome here should be considered a symptom of generalized scleroderma. At present the patient shows the third stage of Raynaud's syndrome—the symptom of previous asphyxia. He now has gangrene, but on observing his skin I see a peculiar destruction of pigment, with white spots. The skin is in a state of edema; he has a masklike face, and I wonder if this will not develop into generalized scleroderma.

Dr. David Bloom: The patient presents the typical syndrome of Raynaud's disease, namely, a history of the fingers' turning white and then blue on exposure to cold and finally the development of gangrene. In cases of progressive symmetric scleroderma such a definite history of color changes is not present.

Dr. Frank Vero: I believe that the patient has Raynaud's disease. I failed to see any signs of scleroderma. The right hand shows pseudosclerodermatous changes, which are frequently seen in Raynaud's disease.

Dr. Max Scheer: Sclerodermatous changes in the later stages of Raynaud's disease are not uncommon. The interesting feature in this case is the eruption on the trunk, especially on the chest and back, where there are many small depigmented macules, about ¼ inch (0.6 cm.) in diameter. It has been suggested that

there may be a localized form of scleroderma (scleroderma guttatum). Whether that is the case here or not, I am unable to say. The patient consulted me only two or three days ago, and I have not had a chance to make any investigations.

A Case for Diagnosis (Parapsoriasis en Plaques?). Presented by DR. LOUIS TULIPAN.

E. J., a man aged 26, states that an eruption appeared six years ago on the elbows, in the axillas and in the inguinal regions and spread to the lower part of the abdomen and the thighs. The eruption then cleared up completely except on the abdomen and anterior surfaces of the thighs.

On these areas there are elongated patches, pale pink, covered by a fine scale, not infiltrated and not pruritic. These areas show no sign of scratching. Histologic examination of a section of the affected skin showed only inflammatory tissue.

DISCUSSION

DR. MAX SCHEER: I think the diagnosis as made by the presenter is the only one that can be made clinically at this time.

DR. CHARLES WOLF: One feature this man presents which is unusual in parapsoriasis en plaques is the patches which have appeared on other parts of his body and which, if his statement is taken as fact, have disappeared. I am inclined to believe that parapsoriasis is a progressive disease, most obstinate to any type of therapy, and rarely disappears spontaneously. The lesions the patient presents at present are not the type of dermatosis seen in parapsoriasis. They are too sharply demarcated. The disease may well be dermatitis venenata. A diagnosis of parapsoriasis, unless backed by histologic study, cannot be accepted.

DR. EUGENE TRAUGOTT BERNSTEIN: This case shows practically all the earmarks of parapsoriasis en plaques. If the patient has had the disorder for six years I do not think all the patches should be stationary. One should accept the diagnosis readily because of the morphologic attributes; the patches are sharply circumscribed. I do not see what other diagnosis can be made.

Larva Migrans. Presented by DR. LAIRD S. VAN DYCK.

C. D. P., a man aged 48, an accountant, first noticed an "itchy pimple" ten days ago on the back of the fourth toe of the left foot. He applied tincture of iodine and several days later noticed a lesion on the plantar surface. He had spent the previous two weeks on the beach at Daytona Beach, Fla., most of the time barefooted.

On the left sole is a tortuous, red, linear lesion extending transversely from the base of the fifth toe to the region of the first metatarsophalangeal joint.

LOS ANGELES DERMATOLOGICAL SOCIETY

L. F. X. WILHELM, M.D., *President*

ARTHUR FLETCHER HALL, M.D., *Secretary*

Oct. 13, 1942

A Case for Diagnosis (Lupus Erythematosus?). Presented by DR. ANKER K. JENSEN.

G. A., a 38 year old white woman, about seven months ago, after an attack of herpes zoster that was limited to the trunk, noticed a small lesion on the forehead. There has been no change in this lesion since it first appeared; it is

on the upper central part of the forehead, a little smaller than a dime. It is erythematous, smooth, well marginated and with what appears to be a slight degree of atrophy in the center. The Wassermann reaction was negative. Slight improvement has followed four roentgen ray treatments of 75 r each.

DISCUSSION

DR. CHRIS HALLORAN: There was considerable atrophy. The disease impressed me as being lupus erythematosus.

DR. MAXIMILIAN OBERMAYER: I agree with Dr. Halloran that the clinical impression is that of lupus erythematosus. This diagnosis, however, is not supported by histologic evidence. The histologic changes are those of lichen planus.

DR. KENDAL FROST: I could not make a diagnosis of lupus erythematosus from the histologic picture. There was infiltration in the corium and little infiltration in the epidermis. I think it is difficult to differentiate between lupus erythematosus and lichen planus histologically in some cases.

DR. SAUL ROBINSON: I believe the patient has atrophic lichen planus.

DR. H. C. L. LINDSAY: I think the diagnosis is between pemphigus and lupus erythematosus. The patient had pemphigoid lesions, and this lesion looks like lupus erythematosus. I wonder if she could not have the Senear-Usher syndrome.

DR. ARTHUR FLETCHER HALL: I do not understand what Dr. Lindsay means regarding pemphigoid lesions in this case. Just because the patient had herpes zoster on the trunk, I do not see why the Senear-Usher type of pemphigus should be considered.

DR. WILLIAM GOECKERMAN: I should lean toward a diagnosis of lichen planus.

DR. SAMUEL AYRES: It is hard to make a positive diagnosis on the evidence available. The disease is more likely to be lupus erythematosus. A simple lesion of lichen planus, especially on the forehead, is unusual. I do not think one can draw any conclusions from examination of this lesion.

Sarcoid of Boeck(?). Presented by DR. SAMUEL AYRES JR.

A. S. P., a 54 year old white man, well nourished, has suffered from his present eruption for about a year and a half. It is rather widely distributed, occurring for the most part on the legs, the knees, the top of the left foot, the back of the left hand, the wrists and the forearms and to a slight extent the trunk. The lesions consist of dime-sized to quarter-sized, sharply circumscribed, brownish red, somewhat elevated, rather shiny, almost waxy-looking plaques. In places there is a tendency for slight central clearing and accentuation of borders. The Wassermann reaction was negative.

DISCUSSION

DR. SAUL ROBINSON: My impression is that the lesion is keloidal. I should reserve the diagnosis until a histologic section is made.

DR. CHRIS HALLORAN: I thought of Kaposi's hemorrhagic sarcoma, but I favor the diagnosis of sarcoid of Boeck.

DR. KENDAL FROST: I think it is difficult to differentiate between the two. There is something about one or two of those lesions that suggests a xanthomatous change.

DR. H. C. L. LINDSAY: Induration in that lesion is decided. I never felt a sarcoid as hard as that.

DR. MAXIMILIAN OBERMAYER: Were roentgenograms of the lungs and the phalanges of the hands and feet taken?

DR. SAMUEL AYERS: No.

Rosacea Improved by Sulfanilamide. Presented by DR. H. C. L. LINDSAY.

I. M. B., a 25 year old white woman, states that she has never had adolescent acne but that the tip of her nose began to get red about six and one-half years ago. This redness with some pustule formation soon affected the alae and the cheeks but not the forehead or the chin. The eruption continued as a persistent rosacea until June 1942, when sulfanilamide treatment was started. Before that, little improvement had followed the use of dilute hydrochloric acid, ultraviolet irradiation and roentgen ray therapy. She has had an "adolescent type" of goiter for the past ten years, for which she has taken iodine and thyroid. Two years ago she suffered from "congestion of the tubes," followed by scanty menstruation, which responded satisfactorily to diethylstilbestrol.

Since June 1942 she has been taking sulfanilamide, 5 grains (0.3 Gm.) twice daily; improvement at once became evident and has continued to an estimated degree of 70 per cent.

DISCUSSION

DR. KENDAL FROST: What did she look like before sulfanilamide was given? She looks pretty bad now.

DR. PAUL FOSTER: Has a gastric analysis or a test for Demodex been made?

DR. H. C. L. LINDSAY: I estimate that she has improved two thirds, and most of the improvement has been since she has been given sulfanilamide.

DR. STANLEY CHAMBERS: What is the presenter's theory in this case?

DR. H. C. L. LINDSAY: The patient has had ovarian trouble and lack of proper menstruation for some time. Sulfanilamide might have cleared up some obscure process there.

DR. ARTHUR FLETCHER HALL: I cannot see how a dose of 5 grains twice a day could have any bacteriostatic effect. I asked the patient when most of the improvement occurred, and she thought that it was in the first two weeks; during the first two weeks the sulfanilamide made her "sick at her stomach." I wonder if limiting her diet when she was nauseated might have had something to do with the improvement.

DR. H. C. L. LINDSAY: I have presented 2 cases in which the disease cleared up from the use of sulfanilamide. One was an instance of lupus erythematosus and the other of chronic eczema of ten years' standing. This patient has acne rosacea. It does not make any difference what the theory is, the result is good. The important point is that one can get good results with small doses of sulfanilamide.

Melanosis of Riehl. Presented by DR. NELSON PAUL ANDERSON.

G. H., an apparently healthy 30 year old white man, has been working as a machinist's helper and living on a deficient diet for the past six months. About five months ago a retiform pigmentation of variable shades of brown was first noticed. At present it varies from reddish to grayish brown. Follicular keratoses are also present, which are most evident on the backs of the hands and fingers. The mucous membranes and scleras are nonpigmented. There is no keratoderma of the soles or palms. Physical examination showed no other abnormalities.

A biopsy was made. Throughout the upper part of the cutis the lymph and blood vessels were dilated and there was a moderate cellular infiltrate composed of round and many wandering connective tissue cells. The pigment present was both extracellular and intracellular (chromatophores). The basal cell margin was disturbed, and the epidermis showed signs of edema. Many of the epidermic cells were hydropic.

DISCUSSION

DR. WILLIAM GOECKERMAN: I heartily agree with the diagnosis. Evidently the patient has been freely exposed to hydrocarbons.

DR. SAUL ROBINSON: I think the diagnosis is correct. I observed 2 cases presented by Dr. Riehl Jr.

DR. ARTHUR FLETCHER HALL: My knowledge regarding Riehl's melanosis is entirely too sketchy for me to discuss this case. It happens, however, that this morning I had occasion to observe a case of proved hemochromatosis. The color was almost exactly that of Dr. Anderson's patient, whose liver I thought I felt a good 2 inches (5 cm.) below the costal margin. May I ask if urinalysis, blood studies and prussian blue stains for iron in the skin have been carried out?

DR. NELSON PAUL ANDERSON: I think that when one looks through the literature on pigmentation from oils and hydrocarbons every dermatologist gives it a different name. Hoffman called the condition melanodermatitis toxicans. The result is that each dermatologist has a different idea of Riehl's melanosis. No matter what name the eruption is called, the man presents a cutaneous picture that is pigmentary and accompanied by atrophic changes in the skin. He was on an inadequate diet and was not exposed to sunlight. The blood sugar content and the urine are normal, and the microscopic examination of the skin is compatible with the diagnosis. In the last ten years at the Los Angeles County Hospital there have been many cases in which a clinical diagnosis of hemochromatosis was made. However, in only 1 case was iron revealed by staining with prussian blue. Many more of these pigmentary dermatoses due to contact with oils will probably be seen.

Lupus Erythematosus in Red Part of Tattooed Area. Presented by DR. ARTHUR FLETCHER HALL.

J. M., a 35 year old Bohemian, an upholsterer, was tattooed on the flexor aspect of the right forearm nineteen years ago. The tattooed area healed normally, and nothing unusual was noticed until three years ago, when roughness of the surface of the red areas developed. These areas have more recently become elevated. The right arm now presents a fairly large shield type of tattoo in red, green and blue. The areas of green and blue appear normal, but every area where red pigment has been tattooed, no matter how small, is uniformly elevated and shows a uniform stippling with dilated follicular openings filled with keratotic plugs, giving a hard, rough surface. The area from which the biopsy specimen was removed with surgical diathermy (with procaine hydrochloride infiltration) is smooth and pink.

The histologic picture was consistent with, but not characteristic of, lupus erythematosus. Slight improvement (less elevation and roughness) has followed five intramuscular injections of crude liver extract, 5 units each, five intramuscular injections of bismuth subsalicylate, 0.26 Gm. each, and four intravenous injections of gold sodium thiosulfate, 25 to 50 mg. each.

DISCUSSION

DR. CHRIS HALLORAN: This is the second case in which I have observed lupus erythematosus developing in the red part of a tattoo. The red part in a tattoo mark is done with mercury; the effect of sunlight is superimposed on the mercury. There was a man at the Los Angeles County Hospital who had lupus erythematosus develop first in a mercury-tattooed area and then in the flush area of the cheeks. Why does mercury in other forms not cause lupus erythematosus? I think this case is extremely interesting.

DR. SAMUEL AYRES: If those lesions had occurred on the face instead of on the tattooed area one could not help but make a diagnosis of lupus erythematosus. I cannot see how the mercury could be responsible for them. Bismuth and mercury compounds are used in the treatment of lupus erythematosus.

DR. WILLIAM GOECKERMAN: I cannot accept a diagnosis of lupus erythematosus without other evidence.

DR. MAXIMILIAN OBERMAYER: I do not think that a definite diagnosis of lupus erythematosus can be made from the histologic changes. A dermatosis in

which the isomorphous irritation effect (Koebner's phenomenon) is known to occur would be more likely to involve a tattoed area.

DR. NELSON PAUL ANDERSON: Clinically this eruption is suggestive of lupus erythematosus. Histologically it is also suggestive in certain ways; i. e., the cellular infiltrate is sharply demarcated at its lower level. I think the diagnosis might be changed to lupus-erythematosus-like reaction in a tattoo mark. I should like to see the patient given patch tests with ammoniated mercury, cinnabar and other mercurial preparations. In some cases of reactions in tattoo marks there is a definite sensitivity to mercury. I feel certain that an intramuscular injection of mercury would cause an exacerbation of lesions. Do you think this reaction is a dermal sensitivity or an epidermal sensitivity?

DR. ARTHUR FLETCHER HALL: There is one thing that no one mentioned: The patient lived with this tattoo mark for sixteen years and then suddenly had this reaction in the areas where the red was tattooed. Dr. Ayres said that if this reaction were seen on the face he would not hesitate to call it lupus erythematosus; if I saw it on the leg I should call it hypertrophic lichen planus. Histologically it might suggest hypertrophic lichen planus just as much as lupus erythematosus.

DR. H. C. L. LINDSAY: Are there any other lesions on the body?

DR. ARTHUR FLETCHER HALL: Just below the left patella is a small group of hyperkeratotic follicular openings; they do not impress me as being part of the same disease. There is no elevation and no inflammatory reaction in that area.

DR. L. F. X. WILHELM: Was the patient unduly exposed to the sun three years ago?

DR. ARTHUR FLETCHER HALL: He had worked with a road gang, but not within two or three years before the onset.

Book Reviews

Medical Parasitology. By James T. Culbertson, Assistant Professor of Bacteriology, College of Physicians and Surgeons, Columbia University. Price, $4.25. Pp. xvi, plus 285. New York: Columbia University Press, 1942.

It could scarcely be expected that a general treatise on parasitology confined to 285 pages would be adequate for the needs of the dermatologist. Not alone are the clinical features too sketchy, but the data on the parasites themselves are far less complete than those in newer dermatologic texts. The index is sketchy too; for example, "scabies" does not appear in it, and "hookworm" carries the reader only to an incidental reference to that subject. It is true that most of the newer dermatologic subjects have been included, such as schistosomiasis, but such a curious condition as Notoedres infestation in man (page 247) is not amplified for the reader by a reference in the literature. In short, for the dermatologist the text can serve only as a setting for the animal parasites in which he is particularly interested.

The photographic illustrations are excellent, and some of them depict features that do not appear in other texts. The outline drawings, too, are well chosen and arranged for the purposes of the student.